22 May 2025
EMA/CHMP/86925/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ezmekly

International non-proprietary name: mirdametinib

Procedure No. EMEA/H/C/006460/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
1-D	One dimensional
2-D	Two-dimensional
ADME	Absorption, distribution, metabolism, and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
Aef	Excreted amount in faeces
Aeu	Excreted amount in urine
AI	Accumulation index
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ARA	Acid-reducing agent
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-12	AUC from dosing to 12 hours post dose
AUC0-12,ss	Steady-state AUC from dosing to 12 hours post dose
AUC0-∞	Complete drug exposure, extending from 0 to infinity
AUC0-t	AUC from zero to the time of the last quantifiable concentration
AUCinf	AUC from dosing extrapolated to infinity
AUClast	AUC from dosing to last quantifiable concentration
AUCtau	AUC for a single dosing interval
AUCtau,ss	Steady-state AUC for a single dosing interval
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BICR	Blinded independent central review
BID	Twice daily
BMI	Body mass index
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BSA	Body surface area
Cavg,ss	Average concentration in each dosing interval at steady state
CDK4	Cyclin-dependent kinase 4
CES	Carboxylesterase
CEP	Certificate of Suitability of the EP
CI	Confidence interval
Clast	Last quantifiable concentration
CLCR	Creatinine clearance
CL/F	Apparent total body clearance of drug from plasma after oral administration
CLm/F	Apparent clearance of the metabolite
Cmax	Maximum concentration
Cmaxss	Steady-state maximum concentration
Cmax,u	Unbound maximum concentration
Cmin	Minimum concentration
COVID-19	Coronavirus disease-19
CPK	Creatine phosphokinase
CQA	Critical Quality Attribute
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DoR	Duration of response
EC	European Commission
ECG	Electrocardiogram
EMA	European medicines agency
E-R	Exposure-response
ERK	Extracellular regulated kinases
ESRD	End-stage renal disease
FDA	Food and Drug Administration

Fef	Fraction excreted in faeces
Feu	Fraction excreted in urine
Fm	Fraction of parent drug converted to metabolite
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCL	Hydrochloric Acid
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IC50	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IIV	Inter-individual variability
IIR	Investigator-initiated research
IR	Infrared
KF	Karl Fischer titration
L	Liter
LDPE	Low density polyethylene
LS	Least-squares
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
λz	Terminal rate constant
m	Meters
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MATE	Multidrug and toxin extrusion protein
MEC	Molar extinction coefficient
MEK	Mitogen-activated protein kinase kinase
MO	Major objection
MPNST	Malignant peripheral nerve sheath tumour
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National cancer institute
ND	No data
NF1	Neurofibromatosis type 1
NHANES	National Health and Nutrition Examination Survey
NMR	Nuclear Magnetic Resonance
NRS-11	Numeric Rating Scale-11
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
PD	Progressive disease
PD-0325901	Mirdametinib
PedsQL	Paediatric Quality of Life Inventory
pERK	phospho-extracellular regulated kinase
Ph. Eur.	European Pharmacopoeia
P-gp	P-glycoprotein
PII	Pain Interference Index
PN	Plexiform neurofibroma
PopPK	Population pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
QD	Once daily
QTc	Corrected QT interval
QTTP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
REiNS	Response Evaluation in Neurofibromatosis & Schwannomatosis
RH	Relative Humidity

RP2D	Recommended Phase 2 dose
rpm	Revolutions per minute
RUV	Residual unexplained variability
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical analysis plan
SAT	Single Arm Trial
SCS	Summary of clinical safety
SmPC	Summary of Product Characteristics
SOB	Specific obligation
StD	Standard deviation
TEAE	Treatment emergent adverse event
TGI	Tumour growth inhibition
TKI	Tyrosine Kinase Inhibitor
Tlast	Time of the last quantifiable concentration
Tmax	Time of the maximum concentration
TSE	Transmissible Spongiform Encephalopathy
T1/2	Terminal half-life
UGT	Uridine diphosphate glucuronosyltransferase
URTI	Upper respiratory tract infection
UV	Ultraviolet
Vz/F	Apparent volume of distribution
WBC	White blood cells
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SpringWorks Therapeutics Ireland Limited submitted on 24 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Ezmekly, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 9 November 2023.

Ezmekly, was designated as an orphan medicinal product EU/3/19/2184 on 25/07/2019 in the following condition: treatment of neurofibromatosis type 1.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ezmekly as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Ezmekly.

The applicant applied for the following indication:

Ezmekly as monotherapy is indicated for the treatment of adult and paediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0223/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0223/2024 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

The applicant applied for a full marketing authorisation, but during the assessment, in response to CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.3. New active substance status

The applicant requested the active substance mirdametinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Karin Janssen van Doorn

The application was received by the EMA on	24 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	18 November 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	21 February 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	1 April 2025
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	29 April 2025

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	13 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ezmekly on	22 May 2025
The CHMP adopted a report on similarity of Ezmekly (Midametinib SpringWorks Therapeutics) with Koselugo on	22 May 2025
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation for the medicinal product Ezmekly (mirdametinib) with the following therapeutic indication:

"Ezmekly as monotherapy is indicated for the treatment of adult and paediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN)."

2.1.2. Epidemiology and risk factors, screening tools/prevention

NF1 is an autosomal dominant genetic disorder with an annual birth incidence of approximately 1 in 2500 individuals worldwide. Approximately half of the cases are inherited, with the remainder being the result of de novo mutations in the NF1 tumour suppressor gene, located at chromosome 17q11.2 (Evans et al. 2010[1]; Ledbetter et al. 1989[2]; Feldkamp et al. 1998[3]). A systematic review and meta-analysis consisting of 10 publications of NF1 incidence and prevalence across the European Union, United Kingdom, Israel, and Cuba showed a similar NF1 birth incidence of 1 in 2,662 (95%CI: 1 in 1,968-1 in 3,601) and prevalence of 3.16 cases per 10,000 (1 in 3,164 [95%CI: 1 in 2,132-1 in 4,712]) (Lee et al. 2023[4]).

2.1.3. Biologic features - Aetiology and pathogenesis

NF1 is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2), which encodes the tumour suppressor protein neurofibromin 1. Neurofibromin 1 is a guanosine 5'-triphosphate (GTP)ase activating protein that promotes the conversion of active Rat Sarcoma Virus (RAS) GTP to inactive RAS guanosine 5'-diphosphate, thereby functioning as a negative regulator of the RAS proto oncogene, which is a key signalling molecule in the control of cell growth. NF1 mutation that leads to loss of function results in a failure to inactivate RAS. Affected individuals start life with 1 mutated (non-functional) copy and 1 functional copy of NF1 in every cell in their body. Although many of the clinical features of this syndrome are apparent from birth, complete loss of gene function is needed for formation of tumours (including PN), by acquisition of a somatic NF1 mutation in selected cells.

Patients with NF1 have an increased risk of developing tumours of the central and peripheral nervous system. Plexiform neurofibromas (PN) are one of the most common benign tumours which occur in approximately 20% to 50% of NF1 patients (Miller et al. 2019[5]).

Neurofibromas are histologically benign nerve sheath tumours, which can be broadly grouped into dermal neurofibroma or PN. Dermal neurofibromas originate from terminal nerve branches in the skin, rarely developing before puberty, whereas PNs typically grow along large nerves and plexuses and are present at birth. PN manifestations vary and may continue to become apparent through late

[1] Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lalloo F. Birth Incidence and Prevalence of Tumour-Prone Syndromes: Estimates from A UK Family Genetic Register Service. Am J Med Genet A. 2010 Feb;152A(2):327-32. doi: 10.1002/ajmg.a.33139. PMID: 20082463.
[2] Ledbetter DH, Rich DC, O'Connell PO, et al. Precise localization of NF1 to 17q11.2 by balanced translocation. American Journal of Medical Genetics. 1989;44(1):20–24.
[3] Feldkamp MM, Gutmann DH, Guha A. Neurofibromatosis Type 1: Piecing the Puzzle Together. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques. 1998;25(03):181-191. doi:10.1017/s0317167100033990
[4] Lee TJ, Chopra M, Kim RH, et al. Incidence and prevalence of neurofibromatosis type 1 and 2: a systematic review and meta-analysis. Orphanet J Rare Dis. 2023;18(1):292. doi:10.1186/s13023-023-02911-2
[5] Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children with Neurofibromatosis Type 1. Pediatrics. 2019;143(5):e20190660

adolescence and early adulthood. Typical PNs are clinically distinct from localised (or 'nodular' or 'atypical') neurofibromas in that they have potential for malignant transformation and are considered by some to be pre-malignant. PN can have complex shapes and sometimes reach very large size, with some documented as being 20% of body weight. PNs may develop along nerves anywhere in the body, and may be located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, and neurological dysfunction.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

NF1 is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. The manifestation of the NF1 clinical diagnostic criteria typically appear in the order of café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and finally neurofibroma.

Longitudinal retrospective review studies have demonstrated age-dependent differences in PNs, with high inverse correlation of PN growth to patient age. One analysis demonstrated the growth rate of tumours in patients <10 years of age was significantly greater than that of tumours in patients >10 years of age (Tucker et al. 2008). Similarly, an observational study of 49 patients aged 3 to 25 years (median 8.3 years), observed that PN volume increased more rapidly than body weight over time ($p = 0.026$; Dombi et al. 2007) and there was a tendency for patients younger than the median age of 8.3 years to have a greater increase in PN volume per year vs older children; 21.1% vs 8.4% volume change per year, respectively ($p = 0.001$). In summary, these findings indicate that the growth rate of PNs in NF1 patients differs by age and supports the independent analysis of volumetric response in adult and paediatric participants.

2.1.5. Management

The treatment approach for the various tumours associated with NF1 depends upon the type of tumour, its effect on adjacent tissues, and related complications. There is one available systemic treatment: selumetinib (Koselugo, EMEA/H/C/005244/0000), an oral selective MEK inhibitor that is approved since 19 June 2021 in Europe for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above. It is approved in the US for the treatment of paediatric patients ≥2 years with NF1 who have symptomatic, inoperable PNs.

There are currently no approved treatments indicated for adults or children with NF1 PN under 3 years of age in Europe.

2.2. About the product

Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). Mirdametinib blocks MEK activity and the rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-MEK pathway. Therefore, MEK inhibition blocks proliferation and survival of tumour cells in which the RAF-MEK-extracellular related kinase (ERK) pathway is activated.

The final indication is:

"Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above."

Treatment with Ezmekly should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

Posology

The recommended dose of Ezmekly is 2 mg/m^2 of body surface area (BSA), twice daily (approximately every 12 hours) for the first 21 days of each 28-day cycle. The maximum dose is 4 mg twice daily (see Table 1).

For paediatric patients from 2 to <6 years of age and for patients who are unable to swallow capsules whole, Ezmekly is also available as a 1 mg dispersible tablet formulation that can be dispersed in water. The recommended dose for patients with a BSA less than 0.40 m^2 has not been established.

Table 1: Recommended dose based on body surface area

Body surface area (BSA)	**Recommended dose**
0.40 to 0.69 m^2	1 mg twice daily
0.70 to 1.04 m^2	2 mg twice daily
1.05 to 1.49 m^2	3 mg twice daily
≥ 1.50 m^2	4 mg twice daily

Duration of treatment
Treatment with Ezmekly should continue until PN progression or the development of unacceptable toxicity.

Missed dose
If a dose of Ezmekly is missed, an additional dose is not to be taken. The patient should continue with the next scheduled dose.

Vomiting
If vomiting occurs after Ezmekly is administered, an additional dose is not to be taken. The patient should continue with the next scheduled dose. Manage events of vomiting as clinically indicated, including use of anti-emetics

Dose adjustments
Interruption and/or dose reduction or permanent discontinuation of Ezmekly may be required based on individual safety and tolerability. Recommended dose reductions are given in Table 2. Permanently discontinue treatment in patients unable to tolerate Ezmekly after one dose reduction.

Table 2: Recommended dose reductions

Body surface area (BSA)	**Reduced dose**	
	Morning	**Evening**
0.40 to 0.69 m2	1 mg once daily	
0.70 to 1.04 m2	2 mg	1 mg
1.05 to 1.49 m2	2 mg	2 mg
≥ 1.50 m2	3 mg	3 mg

Management of patients according to the adverse reactions associated with this medicinal product are presented in Table 3.

Table 3: Recommended dose modifications for adverse reactions

Severity of adverse reaction[a]	**Recommended dose modification for Ezmekly**
Ocular toxicity	
Grade ≤ 2	Continue treatment. Consider ophthalmologic examinations every 2 to 4 weeks until improvement.
Grade ≥ 3	Interrupt treatment until improvement. If recovery occurs ≤14 days, resume at reduced dose (see Table 2). If recovery occurs in >14 days, consider discontinuation.
Asymptomatic retinal pigment epithelium detachment (RPED)	Continue treatment.
Symptomatic RPED	Interrupt treatment until resolution. Resume at reduced dose (see Table 2).
Retinal vein occlusion (RVO)	Discontinue treatment permanently.
Decreased left ventricular ejection fraction (LVEF)	
Asymptomatic, absolute decrease in LVEF less than 20% from baseline and is greater than the lower limit of normal	Continue treatment.
Asymptomatic, absolute decrease in LVEF of 10 % or greater from baseline and is less than the lower limit of normal.	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
For any absolute decrease in LVEF 20 % or greater from baseline.	Discontinue treatment permanently.
Skin toxicity	
Grade 1 or 2 dermatitis acneiform or non-acneiform rash	Continue treatment.
Intolerable Grade 2 or Grade 3 dermatitis acneiform or non-acneiform rash	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Grade 3 or Grade 4 dermatitis acneiform or non-acneiform rash	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Other adverse reactions	
Intolerable Grade 2 or Grade 3	Interrupt treatment until improvement. Resume at reduced dose (see Table 2).
Grade 4	Interrupt treatment until improvement. Resume at reduced dose (see Table 2). Consider discontinuation.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that:

- based on the available information, it was uncertain whether the limited data package (both in

terms of study design and number of patients) would enable to conclude on a positive benefit/risk and thereby fulfil the unmet medical need
- the clinical relevance of the observed activity was uncertain considering the large heterogeneity in the natural course of the disease in the context of a single arm trial and the uncertainty regarding the validity of the provided external controls.

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

Mirdametinib has shown efficacy in adults and paediatric NF1 patients aged 2 years of age and older with symptomatic PN. In the pivotal study MEK-NF-201, the confirmed objective response rate (ORR) assessed by blinded independent central review (BICR) demonstrated evidence of treatment effect for both the paediatric and adult cohorts with confirmed ORR (95% confidence interval [CI]) of 51.8% (38.0, 65.3; null hypothesis 20%) and 41.4% (28.6, 55.1; null hypothesis 23%), respectively. Responses were durable with 89.7% of the paediatric responders and 87.5% of the adult responders maintaining their objective response for at least 12 months, as of the data cut-off of 12Jun2024 (MEK-NF-201 CSR Addendum). When compared with the natural history control described in MEK-NF-201 Natural History Report, mirdametinib displayed significant decreases in yearly percentage change in the target PN volume, whereas the patients in the historical control experienced increases in median PN volume. Improvements in quality of life, pain severity, and pain interference as assessed by patient-reported outcomes were also observed at the prespecified Cycle 13 timepoint, supporting clinical benefit of mirdametinib in participants with NF1 PN. Thus, the efficacy data for Study MEK-NF-201 indicate a favourable benefit for patients treated with mirdametinib.

The safety profile in Study MEK-NF-201 is manageable and acceptable for the use of mirdametinib for the treatment of adult and paediatric patients aged ≥2 years with NF1 PN. Mirdametinib has been studied in 133 patients with NF1 PN, including 58 paediatric and 75 adult participants with a safety profile consistent with mitogen-activated protein kinase (MEK) inhibitors (Solares 2021, Subbiah 2020). The safety population included in Study MEK-NF-201 is representative of the intended real-world population of patients with NF1 PN (Copley-Merriman 2021), so the observed safety profile can reasonably be expected to reflect the safety profile observed when mirdametinib is used to treat patients with NF1 PN following market authorisation.

The overall benefit-risk assessment for mirdametinib in participants with NF1 PN is favourable, demonstrating a statistically significant ORR, coupled with statistically significant and clinically meaningful improvements in health-related quality of life, pain severity, and pain interference, and an acceptable safety profile in paediatric and adult patients. Data from a more recent cut-off (12Jun2024) demonstrate that the positive benefit-risk assessment is maintained with longer follow-up.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant proposed to commit to the following specific obligations (SOBs) in order to provide comprehensive data:

  - Efficacy and safety data from the pivotal Study MEK-NF-201 with a longer follow-up. At the original Study MEK-NF-201 data cut-off (20Sep2023), the median (min, max) duration of mirdametinib exposure was 21.8 (0.4, 45.6) months.
  - The applicant proposes an additional data cut-off on 22Dec2028 that will provide an additional 5 years of follow-up data.
  - Safety data from a non-interventional post-authorisation safety study (PASS). The PASS patient population is planned to include NF1 patients in the European Union (EU) and the

United States with symptomatic PN who have been prescribed at least one dose of mirdametinib and who are aged ≥2 years at the start of treatment.

- Unmet medical needs will be addressed, as there is no authorised treatment for paediatric patients between 2 and 3 years of age, nor for adult patients.

There is no formulation available for patients unable or unwilling to swallow the capsule whole. Koselugo has been granted a conditional marketing authorisation in the EU for the treatment for paediatric patients aged ≥3 years. In this patients population, the applicant claimed that mirdametinib could potentially address the same unmet medical needs, to a similar or greater extent than Koselugo: the comparison of the results from study MEK-NF-201 to the SPRINT data suggests that mirdametinib has numerically higher confirmed BICR ORR compared with Koselugo (ICR) with a deeper median best average percent change from baseline tumour volume (median best average percentage change from baseline in target PN tumour volume of -41.8% and a maximum reduction of -91% for mirdametinib versus a median of -22.05% and maximum reduction of -53.7% with selumetinib). Mirdametinib demonstrated a better safety and tolerability profile compared with selumetinib, with a lower rate of Grade ≥3 treatment-emergent adverse events (39.3% vs 62%) and serious adverse events (14.3% vs 24%), and a lower rate of dose interruptions (30.4% vs 80%) and dose reductions (12.5% vs 24%).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required:

Given the lack of an age-appropriate formulation and the safety concerns leading to dose interruptions and dose reductions associated with the only currently available systemic therapy for paediatric patients, as well as no treatment indicated for paediatric patients between 2 and 3 years of age or adults with NF1 PN being approved, the benefits to public health of the immediate availability of mirdametinib outweigh the risks.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented in two formulations and is available as hard capsules or dispersible tablets. The capsules are available in two strengths containing either 1 mg or 2 mg of mirdametinib, while the dispersible tablets contain 1 mg of mirdametinib.

The capsule other ingredients are:

Capsule content: microcrystalline cellulose (E460), croscarmellose sodium (E468), magnesium stearate (E572). Capsule shells: gelatin (E441), titanium dioxide (E171), yellow iron oxide (E172), brilliant blue (E133). Printing ink: potassium hydroxide (E525), propylene glycol (E1520), purified water, shellac (E904), titanium dioxide (E171).

The dispersible tablet other ingredients are:

Microcrystalline cellulose (E460), croscarmellose sodium (E468), sucralose (E955), magnesium stearate (E572), grape flavour [dried glucose liquid, natural flavour, modified corn starch (E1422), triacetin (E1518)].

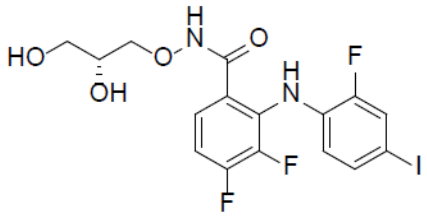
The hard capsules and dispersible tablets are available in a high-density polyethylene (HDPE) bottle, secured with child-resistant closure and aluminium foil induction seal. For the dispersible tablet formulation the HDPE bottle also contains a cotton coil.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of mirdametinib is (R)-N-(2,3-dihydroxypropoxy)-3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzamide corresponding to the molecular formula $C_{16}H_{14}F_3IN_2O_4$. It has a relative molecular mass of 482.20 g/mol and the following structure:

Figure 1: Active substance structure



The chemical structure was elucidated by a combination of IR, NMR, MS & elemental analysis. The solid state properties of the active substance were measured by XRPD.

The active substance is a white to tan or pink powder. It is highly soluble in aqueous conditions and it is non hygroscopic.

Mirdametinib exhibits stereoisomerism due to the presence of one chiral centre. The source of the chiral centre originates in one of the starting materials. A test for chiral purity is included in the specification of the starting material and in the specification of the active substance.

Polymorphism has been observed for mirdametinib. Comprehensive studies demonstrated that there were three potential polymorphic forms related to the non-solvated active substance. The applicant has demonstrated that the manufactured polymorphic form (form IV) is the most thermodynamically stable form. A control for the polymorphic form is also included in the specification of the active substance.

2.4.2.2. Manufacture, characterisation and process controls

Satisfactory information with respect to GMP standards have been provided.

Mirdametinib is synthesised in several main stages using well defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Initially the information provided concerning potential mutagenic impurities was not considered acceptable and a major objection (MO) was raised. As part of this the applicant was requested to update the proposed limits for a number of impurities, to review all potential impurities for mutagenicity, and to justify that the control strategy for potential mutagenic impurities was adequate. To resolve this MO the applicant provided relevant justification for the limits proposed for potential mutagenic impurities, the assessment of potential mutagenicity was revised to consider all potential

impurities and the applicant's control strategy was considered acceptable for the control of such impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The same route of synthesis was maintained during development, and process changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in an LDPE bag which complies with Commission Regulation (EU) 10/2011, as amended. The LDPE bag is placed inside another LDPE bag and this is then placed in a fibre drum.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identification (IR, HPLC), assay (HPLC), impurities (HPLC), chiral purity (HPLC), residual solvents (GC), residual benzene (GC), elemental impurities (ICP-MS), water content (KF), residue on ignition (Ph. Eur.), solid state form (XRPD), particle size (laser light diffraction).

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable. No impurities are present at higher levels than the ICH qualification threshold.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for a number of active substance batches manufactured throughout the development programme were provided including 3 batches at the commercial scale. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three registration batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The registration batches are representative of the commercial process and only a minor difference in one of the steps differentiates the manufacturing process of the registration batches from the commercial batches. In addition to this the applicant provided 12 months of long term data from commercial batches under the same ICH conditions specified above. Supportive stability data was also available from earlier clinical batches. Photostability testing following the ICH guideline Q1B was performed on one batch. Results of stress conditions of exposure to heat in the solid & liquid phase, as well as exposure to acidic, basic and oxidative solution conditions were also provided on one batch.

The following parameters were tested: appearance, assay, related substances, water content, chiral purity and solid state form. The analytical methods used were the same as for release and were stability indicating.

At long term and accelerated conditions all tested parameters were within the specifications and no specific trends were observed. In the stress conditions it was shown that the active substance is sensitive to very high temperatures in the solid and liquid phase, in addition to this degradation occurred under the oxidative conditions and when the active substance was exposed to light. No significant degradation was seen upon exposure to acidic or basic conditions.

With respect to ongoing stability programs any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at room temperature in the proposed container.

2.4.3. Finished Medicinal Product – hard capsules

2.4.3.1. Description of the product and pharmaceutical development

The hard capsules contain 1 mg or 2 mg of mirdametinib and have the following appearance:

1 mg hard capsules: Size 3 (approximately 16 mm × 6 mm) capsule comprised of a light green opaque body and cap with 'MIR 1 mg' printed in white ink on the cap.

2 mg hard capsules: Size 1 (approximately 19 mm × 7 mm) capsule comprised of a white opaque body and a blue-green opaque cap with 'MIR 2 mg' printed in white ink on the cap.

The aim of development for the capsules was to generate an oral solid dosage form suitable for administration to the intended population who could swallow such capsules. For those who could not swallow the capsules, such as the younger paediatric age range, a dispersible tablet was developed and authorisation for this is also sought. For the capsule formulations the quality target product profile (QTPP) and critical quality attributes (CQAs) were defined.

The active substance is highly soluble and is considered BCS class I, one stable polymorphic form (form IV) is produced by the finished manufacturer. The particle size of the active substance is controlled in order to ensure consistency of manufacture and uniformity of dosage units

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. Compatibility between the active substance and the excipients was investigated during development studies and was confirmed by the finished product stability results.

In the clinical studies three different types of oral formulations were used, an oral solution, hard capsules, and dispersible tablets. In the later clinical studies only the capsules and dispersible tablets were investigated. For a full overview of the clinical studies please refer to the clinical sections of this report. With respect to the capsule formulations, the commercial 1 mg and 2 mg strengths are manufactured by the same process and have the same formulation as those in the pivotal clinical studies. Comparative dissolution was also performed between capsule and dispersible tablet formulations at pH 1.2, 4.5 and 6.8. In vitro dissolution similarity was observed between all formulations for which authorisation is sought.

A dry granulation process based on roller compaction was pursued for the manufacture of the capsule formulation, this followed earlier processes which had used a direct slugging method to compress and fill the powder. A common blend approach was chosen for both capsule strengths. During manufacturing process development the applicant optimised the manufacturing process, this included the distribution of excipients in the blending steps, the parameters for blend lubrication and roller compaction. The information gained during development was used to inform the selection of commercial manufacturing process and its operating parameters.

The applicant investigated the discriminatory potential of the dissolution method selected, the operating parameters for the method were selected with the aim to maximise discriminatory potential. The applicant investigated the impact of manufacturing process changes, alteration of formulation

ratios, and the changes to the active substance particle size with respect to the discriminatory ability of the method. The results showed that the dissolution profiles do not change even with such changes. In light of the BCS class I status of the active substance and low content of the formulations it was accepted that the discriminatory nature could not be meaningfully proven. The dissolution results are consistent with the performance of the clinical batches.

The primary packaging is a HDPE bottle secured with child-resistant closure and aluminium foil induction seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

Satisfactory information with respect to GMP standards has been provided.

The manufacturing process consists of six main steps: pre-blending, lubrication, roller compaction and milling, lubrication, encapsulation, & packaging. The process is considered to be a non-standard manufacturing process due to low content of the active substance.

Major steps of the manufacturing process have been validated by a number of studies. Process validation results for three commercial scale batches of each strength have been provided. It has been demonstrated that the manufacturing process is capable of producing finished product of the desired quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (HPLC), content uniformity (Ph. Eur.), water content (KF), microbiological quality (Ph. Eur.).

The specifications for the control of the finished product contains the typical tests for this type of pharmaceutical form and the limits have been adequately justified.

Degradation products are controlled in line with ICH Q3 guidance and there are no degradation products present at levels which exceed the qualification threshold. Initially the provided assessment of potential impurities in the finished product did not sufficiently account for potential mutagenic impurities in line with ICH M7 requirements. An MO was raised on this aspect, and the applicant resolved this by providing an updated assessment outlining that none of the impurities in the finished product were considered to be potentially genotoxic.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The risk assessment of potential presence of nitrosamine impurities was initially not considered acceptable, and an MO was raised as the applicant's risk assessment did not sufficiently take into account all potential risk factors and nitrosamine impurities that could be formed. In addition to this, the assessment of the potential impurity N-nitrosomirdametinib was not considered acceptable. To resolve this MO the applicant provided an updated nitrosamine risk assessment and suitably justified the absence of control for potential N-nitrosomirdametinib. The applicant's proposed acceptable intake for N-nitrosomirdametinib which was 78,000 ng/day based on a read-across approach was considered adequately justified, and the applicant provided data demonstrating that N-nitrosomirdametinib does not readily form under nitrosating conditions. Calculations were also performed to show that from a

theoretical standpoint the conditions in the finished product would not lead to the acceptable intake being exceeded when considering the amount of the active substance and potential nitrosating agents present. Based on the information provided in the response, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for a number of batches this includes 3 commercial scale batches of each strength as well as batches from the clinical study programme, the results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from 3 commercial scale batches of each strength of capsule finished product stored for up to 36 months under long term conditions (25ºC / 60% RH), for up to 12 months under the intermediate condition (30ºC / 66% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, dissolution, water content, & microbiological quality. The analytical procedures used are stability indicating. At long term and intermediate conditions no trends or out of specification results were observed. At the accelerated condition an out of specification result and significant decrease in assay was seen for one batch at the 6 month time-point. The observed out of specification result at accelerated conditions is reflected in the storage conditions proposed for the capsule formulation.

The applicant initially proposed a finished product shelf life which was not adequately supported by long term data and for which the extrapolation could not be accepted based on the out of specification result observed at the accelerated testing condition. An MO was raised to ensure that the shelf-life of the product was adequately set. To resolve this MO the applicant provided further long term stability data and performed extrapolation of the data in line with ICH Q1E requirements. The shelf life proposal was acceptable in light of the further data provided.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A significant increase of the known photo degradation impurity was observed upon exposure to light in the unprotected samples.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 42 months and do not store above 30°C, and store in the original package to protect from light as stated in the SmPC are acceptable.

2.4.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. Finished Medicinal Product – dispersible tablet

2.4.4.1. Description of the product and pharmaceutical development

The dispersible tablet contains 1 mg of mirdametinib and has the following appearance:

Oval, white to off-white dispersible tablets (approximately 6 mm × 9 mm) debossed with 'S' on one side.

The aim of development of the dispersible tablet was to generate an oral solid dosage form suitable for administration to those who could not swallow the capsule dosage form. In particular this would encompass the younger age range of the intended paediatric population. The applicant developed 0.5 mg and 1 mg dispersible tablet formulations however the applicant only submitted the 1 mg strength for authorisation. The dispersible tablets can be dispersed in water or swallowed whole. For the dispersible tablet formulation the quality target product profile (QTPP) and critical quality attributes (CQAs) were defined.

The dispersible tablet was developed using knowledge gained during the development of the capsule formulation. The active substance is highly soluble and is considered BCS class I, and one stable polymorphic form (form IV) is produced by the finished manufacturer. The particle size of the active substance is controlled in order to ensure consistency of manufacture and uniformity of dosage units.

The applicant utilised similar excipients to the capsule formulation, with the addition of sucralose and grape flavour to improve palatability. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards where relevant; the grape flavour is the only non-compendial excipient present. There are no novel excipients used in the finished product formulation. The excipients are suitable for the intended paediatric population. The list of excipients is included in section 6.1 of the SmPC. Compatibility between the active substance and the excipients was investigated during development studies and was confirmed by the finished product stability results.

In the clinical studies three different types of oral formulations were used, an oral solution, hard capsules, and dispersible tablets. In the later stage phase clinical studies only the capsules and dispersible tablets were investigated. For a full overview of the clinical studies please refer to the clinical sections of this report. With respect to the dispersible tablet formulations, the commercial 1 mg strengths are manufactured by the same process and have the same formulation as those in the pivotal clinical studies. Comparative dissolution was also performed between capsule and dispersible tablet formulations at pH 1.2, 4.5 and 6.8. In vitro dissolution similarity was observed between all formulations for which authorisation is sought.

The tablet formulation and manufacturing process were developed based on the capsule formulation. The manufacturing processes both use a dry granulation process, and for the tablets there are additional steps (extra-granular blending, lubrication, and compression) to form a dispersible tablet. Process optimisation during development included the process parameters of the lubrication steps, roller compaction parameters, and compression steps in order to investigate the impact on critical attributes such as assay, uniformity, and dispersibility of the tablets. The information gained during development was used to inform the selection of the commercial manufacturing process and its operating parameters.

The applicant investigated the development of a method for dissolution, which began with the use of the method already developed for the capsules. During this process it became evident that across the physiological pH range dissolution of the tablets was very rapid and showed low variability. Considering the solubility of the active substance and fast dispersion of the tablets it was decided to pursue a disintegration test rather than a dissolution test as a quality control measure. The disintegration step is

considered to be the rate limiting aspect for the release of the active substance from the tablets. The disintegration method is performed as per the Ph. Eur. monograph for dispersible tablets, and the method can differentiate between tablets compressed to different hardness levels.

Instructions on preparing the tablet dispersion are included in the product information (SmPC section 4.2) and the dispersible tablets can also be swallowed whole. The applicant demonstrated that the tablets can be reproducibly dispersed and provided acceptable information on dose recovery when the dispersion is prepared and administered in accordance with the product information. Once the tablets have been dispersed, they can also be used for administration via enteral feeding tubes, and this information is described in the product information.

The primary packaging is a high-density polyethylene (HDPE) bottle, secured with child-resistant closure and aluminium foil induction seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.4.2. Manufacture of the product and process controls

Satisfactory information with respect to GMP standards has been provided.

The manufacturing process consists of seven main steps: pre-blending, lubrication, roller compaction and milling, blending, lubrication, compression, and packaging. The process is considered to be a non-standard manufacturing process due to low content of the active substance.

Major steps of the manufacturing process have been validated by a number of studies. Process validation results for three commercial scale batches of each strength have been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.4.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identity (HPLC, UV), assay (HPLC), degradation products (HPLC), disintegration (Ph. Eur.), fineness of dispersion (Ph. Eur.), content uniformity (Ph. Eur.), water content (KF), microbiological quality (Ph. Eur.).

The specifications for the control of the finished product contains the typical tests for this type of pharmaceutical form and the limits have been adequately justified.

Degradation products are controlled in line with ICH Q3B guidance and the relevant qualification threshold is not exceeded. Initially the provided assessment of potential impurities in the drug product did not sufficiently account for potential mutagenic impurities in line with ICH M7 requirements. An MO was raised on this aspect, and the applicant resolved this by providing an updated assessment outlining that none of the impurities in the drug product were considered to be potentially genotoxic.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The assessment of potential nitrosamine impurities was initially not considered acceptable, and an MO was raised as the applicant’s risk assessment did not sufficiently take into account all potential risk factors and nitrosamine impurities that could be formed. In addition to this, the assessment of the

potential impurity N-nitrosomirdametinib was not considered acceptable. To resolve this MO the applicant provided an updated nitrosamine risk assessment and suitably justified the absence of control for potential N-nitrosomirdametinib. The applicant's proposed acceptable intake for N-nitrosomirdametinib which was 78,000 ng/day based on a read-across approach was considered adequately justified, and the applicant provided data demonstrating that N-nitrosomirdametinib does not readily form under nitrosating conditions. Calculations were also performed to show that from a theoretical standpoint the conditions in the finished product would not lead to the acceptable intake being exceeded when considering the amount of the active substance and potential nitrosating agents present. Based on the information provided in the response, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for a number of batches this includes 3 commercial scale batches of each strength as well as batches from the clinical study programme, the results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.4.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 30 months under long term conditions (25ºC / 60% RH) for up to 9 months under the intermediate condition (30ºC / 66% RH), and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay/degradation products, water content, microbiological quality, disintegration, and fineness of the dispersion. The analytical procedures used are stability indicating. At long term conditions the product was shown to be acceptably stable and no significant changes or out of specification results were observed. At the accelerated condition significant decreases in assay values were observed at the 6 month time-point, this is similar to the behaviour of the capsule formulations, and this is also reflected in the temperature storage conditions proposed for the dispersible tablet formulation.

The applicant initially proposed a finished product shelf life which was not adequately supported by long term data and for which the extrapolation could not be accepted based on the decrease in assay values observed at the accelerated testing condition. An MO was raised to ensure that the shelf-life of the product was adequately set. To resolve this MO the applicant provided further long term & intermediate stability data and performed extrapolation of the data in line with ICH Q1E requirements. The shelf life proposal was acceptable in light of the further data provided.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A significant increase of the known photo degradation product was observed upon exposure to light in the unprotected samples.

The stability of the prepared tablet dispersion in water was also investigated and it was demonstrated that these dispersions were stable for up to 6 hours, which was the maximum amount of time investigated in the study.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Based on available stability data, the proposed shelf-life of 36 months and do not store above 30°C, and store in the original package to protect from light as stated in the SmPC are acceptable.

2.4.4.5. Adventitious agents

No excipients derived from animal or human origin have been used in the dispersible tablet formulation.

2.4.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the assessment there were a number of quality MOs raised, these concerned the assessment of potential mutagenic impurities in the active substance and finished product, the evaluation of potential nitrosamine impurities in the finished product, and the initial proposals for extrapolation of the finished product shelf life. To resolve these objections the applicant provided further information concerning potential mutagenic impurities, and similarly provided further information on potential nitrosamine impurities along with a revised risk assessment. To resolve the objection concerning the finished product shelf life proposal the applicant provided further long term stability data and performed extrapolation in line with published guidance in ICH Q3E.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.7. Recommendation(s) for future quality development

N/A

2.5. Non-clinical aspects

2.5.1. Introduction

Mirdametinib is an orally administered, selective, non-competitive small molecule inhibitor of the dual specific kinases, mitogen-activated protein kinase (MEK)1 and MEK2, being developed for use in patients with neurofibromatosis type 1 (NF1). Two major metabolites of mirdametinib were identified: PD-0315209 is the carboxylic acid metabolite of mirdametinib and the other metabolite, M22 (ASYM-130520) is a secondary O-glucuronide.

The non-clinical programme for mirdametinib was performed according to ICH M3. Rats and dogs were used as relevant species based on PK and metabolism data. A complete genotoxicity battery was performed according to ICH guideline S2. No long-term studies were performed in rats and dogs and

no definitive embryo-foetal development (EFD) and pre- and post-natal development (PPND) studies were performed. A 26-week carcinogenicity study was performed in transgenic mice and a 2-year carcinogenicity study is ongoing (dosing has started in august 2024). Margins of exposure were calculated based on popPK results. Administration in animals are conducted once daily in contrast to the proposed twice daily treatment regimen in patients.

No scientific advice was requested in the EU by the applicant.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

Most of the pharmacodynamic parameters were obtained from the report RR-REG 761-00063 (2003), which contains data published in peer reviewed journals. This report is not a study report or a compilation of study reports, and original reports could not be obtained.

Due to the 80% sequence homology between MEK1 and MEK2 and the conserved binding pocket sequence, mirdametinib's inhibition of both MEK1 and MEK2 has been demonstrated *in vitro* by the Ki of 1 nM against activated MEK1 and MEK2, and by the binding assay's Kd values of 17 nM and 100 nM for MEK1 and MEK2, respectively. MEK1's inhibition has been confirmed in a cellular assay and IC_{50} is determined to be around 0.33 nM in a whole cell (Colon 26) assay.

The cellular activity of S-enantiomer PD 0326116 was 2-fold lower (IC_{50} = 0.82 nM). In clinical studies A4581001 and A4581004, S-enantiomer's exposure was at minimum 11-fold and average between 49- and 65-fold lower than mirdametinib exposure (based on Cmax).

In vitro PD activity of M22 (O-glucuronide metabolite, representing 15% of the total radioactivity) was characterised in 3 cell lines: CT-116 (human), Colon-26 (mouse), and MDCK (dog). M22 was found to be significantly less potent than parent mirdametinib, with a range of IC_{50} values from 362 to 835 nM for M22 compared to 1.5 to 4.8 nM for mirdametinib.

The major human metabolite PD-0315209 (a carboxylic acid metabolite) was reported in the human mass balance study as 24% of the total radioactivity. However, the exposure in patients for the metabolite PD-0315209 at steady state is predicted to be similar to the parent (according to the mirdametinib popPK model). Results are reported in report 761-00063 (same methodology is assumed). The metabolite PD-0315209 presented a comparable potency than its parent against MEK1 (IC50 = 66nM vs 15 nM) but a lower activity in reducing ERK phosphorylation in tumour cell lines (IC50 = 1300 nM vs 0.59 nM). In vivo data (in C26 tumour-bearing animals) revealed a nearly complete suppression of pERK in tumour 2h after dosing, but this effect was not sustained with time contrary to the parent. Metabolite PD-0315209 was found to be significantly less potent than the parent mirdametinib, with a range of IC50 values from 5291 to >10000 nM for PD-0315209 compared with 1.2 to 4.3 nM for mirdametinib across cell lines and incubations times. In addition, human exposure with metabolite PD-0315209 is low (unbound Cmaxss was 1.6 nM). This unbound Cmax level is approximately 810-fold lower than the metabolite PD-0315209 in vitro IC50 for ERK phosphorylation.

In vivo

Mirdametinib was originally developed for the treatment of several cancers and later in the treatment of paediatric patients NF1 and PN. Therefore, numerous in vivo proof of concept *(*POC) models were investigated.

Firstly, mirdametinib was studied in xenografted mice with cancer cell lines. The results demonstrated that mirdametinib exhibited a broad spectrum of in vivo antitumour activity with various level of efficacy against a panel of human tumour xenografts representing human colon, pancreatic, lung, and renal cancers, along with a ZR-75-1 xenograft presumed to be breast-derived. No effect was noted in RXF-393 renal adenocarcinoma.

Later with the change of intended indication, mirdametinib was administrated in a genetically engineered mouse model with the NF1 neurofibroma disease ($Nf1^{fl/fl}$;*Dhh-Cre* mouse model); results were reported from literature (Jessen et al. 2013 and Jousma et al. 2015). In the first study (Jessen et al. 2013), mirdametinib was administrated at 1.5, 5.0, or 10 mg/kg/day orally once a day for 60 to 90 days. Tumours measured by volumetric magnetic resonance imaging analysis were reduced to a similar degree at all 3 dose levels ($p < 0.001$) in >80% of mice, which correlated with associated reductions in biomarkers for cell proliferation (Ki67+) and blood vessels (MECA+ endothelial cells). In the second study (Jousma et al. 2015), mirdametinib was administrated at 0.5 (HED 2.5 mg BID) and 1.5 mg/kg/day (8 mg BID) once daily by oral gavage for 60 days to evaluate if low doses of mirdametinib would still be efficacious. The extent of tumour shrinkage observed in the 0.5 mg/kg mirdametinib group was comparable to the shrinkage of tumours from mice treated in experiment with mirdametinib at 1.5 mg/kg. Similar reductions in blood vessels area were observed between the 2 dose groups. Reductions in biomarkers for cell proliferation (Ki67+) was observed to be dose dependent, with a higher reduction using mirdametinib at 1.5 mg/kg/day.

2.5.2.2. Secondary pharmacodynamic studies

Mirdametinib was tested at 1 µM (1200-fold greater than the unbound plasma Cmax at the intended dose) in a selectivity assay with a panel of 104 kinases. 100 were completely refractory to inhibition after treatment. 4 kinases were inhibited after mirdametinib treatment and showed little to no kinase remaining activity, including the following: MEK1 (21% activity), B-Raf (0% activity), B-Raf V599E (-1% activity), and C-Raf (0% activity). Inhibition of B-Raf and C-Raf kinases is consistent with the nature of the linked assay for a MEK inhibitor as MEK functions downstream of both B-Raf and C-Raf.

Mirdametinib was tested at 1 µM and 10 µM (1200-fold and 12000-fold greater than the unbound plasma Cmax at the intended dose) in a selectivity assay with a panel of 87 targets. Mirdametinib inhibited the L-type calcium channel (phenylalkylamine) by 54% and inhibited the peroxisome proliferator-activated receptor gamma (PPARγ) by 53%. A significant multiple of exposure was observed, but no effect on these 2 targets is awaited at the intended clinical exposure.

No secondary PD screening assay was performed with the metabolite PD-0315209.

2.5.2.3. Safety pharmacology programme

GLP safety pharmacology core battery studies were performed with mirdametinib. Mirdametinib at 100 µM reduced significantly the mean hERG current amplitude by 39.5% (IC50 >100 µM). No significant effect was observed at 10 µM (12000-fold greater than the unbound plasma Cmax at the intended dose). In contrast, the metabolite PD-0315209, at 100 µM, increased the mean hERG current amplitude by 25.6%. No significant effect was observed at 10 µM (largely greater than the unbound plasma Cmax at the intended clinical dose).

Mirdametinib tested at 1, 10, or 100 µM did not affect the resting membrane potential. However, mirdametinib did reduce the action potential duration at both 10 and 100 µM, and Vmax and the amplitude at 100 µM; this effect on cardiac action potential is possibly due to the inhibition of sodium and/or calcium channels. A GLP-compliant study to evaluate the effects of mirdametinib on the cardiovascular parameters of blood pressure, heart rate, and cardiac rhythm in telemetered male

cynomolgus monkeys was conducted. No effect was identified up to 10 mg/kg (20-fold greater than the total plasma mirdametinib Cmax at the intended dose and around the clinical exposure for the metabolite). No effect was identified in the clinical QTC study. No toxic effect on cardiac function was observed in repeated dose toxicity studies in rats and dogs.

The effect of mirdametinib on the CNS function was studied first after oral administration and secondly after IV administration. At 100 mg/kg, vertical movements and the total distance covered decreased by 45% and 30%, respectively, at 24 hours post dose. In addition, observational assessment at 100 mg/kg included salivation and red staining of the muzzle at approximately 1 and 24 hours post dose in 2 animals. A dose-dependent, although statistically not significant, increase in failure in the inverted screen test was observed both at 1 and 24 hours post dose. No CNS effects were observed at 30 mg/kg (27-fold the clinical exposure based on the AUC determined at the clinical intended dose from the popPK modelling). A second study was performed using the IV route up to 150 mg/kg to maximise the exposure (279-fold the clinical exposure based on the AUC determined at the clinical intended dose from the popPK modelling). No effect was observed on the measured parameters (neurofunctional and reflex testing); however, the locomotor activity was not measured in this second study.

Increases in respiratory rate with a decrease of the tidal volume were observed after administration of mirdametinib at 30 mg/kg and 100 mg/kg in rats after single administration. No effect was observed at 10 mg/kg. Although no TK measurements were performed, exposure at 30 and 100 mg/kg could be considered largely above the clinical range predicted at the intended dose. In addition, no respiratory effect was observed in animals at the clinical exposure range. The risk appears therefore low for humans at the intended posology.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

2.5.3. Pharmacokinetics

Overall 20 non-clinical pharmacokinetics studies (i.e. *in vitro* metabolite profiling, CYP inhibition and induction, and P-gp substrate evaluation, protein binding, and others) as listed in Table 4 were conducted.

Table 4: Non-clinical PK studies

Overview			**Test Article:** Mirdametinib
Type of Study	**Test System**	**Method of Administration**	**Study Number**
Absorption			
Caco-2 permeability	Caco-2 cells	In vitro	764-04274
Caco-2 permeability and classification of permeability by BCS	Caco-2 cells	In vitro	23SPRWP2
Equilibrium solubility	Aqueous buffer	In vitro	ASYM-122569
Distribution			
Plasma protein binding and blood-plasma partitioning	CD-1 mouse, Sprague-Dawley rat, beagle dog, cynomolgus monkey, human	In vitro	764-04271

Overview			**Test Article:** Mirdametinib
Type of Study	**Test System**	**Method of Administration**	**Study Number**
Plasma protein binding and blood-plasma partitioning	Human	In vitro	19SPRWP2R1
Metabolism			
Reaction phenotyping	Human recombinant carboxylesterase enzyme supersomes	In vitro	2102065
Cross-species metabolism in liver microsomes and hepatocytes	Rat, dog, monkey, and human	In vitro	764-04904
Metabolism in human liver microsomes	Human liver microsomes	In vitro	2309066-01
Metabolic stability in liver microsomes and UGT reaction phenotyping	Human	In vitro	2009107_2009108
Metabolite identification	Human plasma	In vitro	220563
Metabolite synthesis	NA	In vitro	CDo122569-01
Pharmacokinetic drug interactions			
CYP450 enzyme inhibition	Human liver microsomes	In vitro	764-04278
CYP450 enzyme inhibition	Human liver microsomes	In vitro	764-04279
CYP450 enzyme inhibition	Human liver microsomes	In vitro	764-04863
CYP450 enzyme inhibition	Human microsomes	In vitro	19SPRWP2_CYP IC50
CYP450 enzyme inhibition	Human liver microsomes	In vitro	2103064
CYP450 enzyme induction	Human hepatocytes	In vitro	19SPRWP2_CYP Induction
CYP450 enzyme induction	Human hepatocytes	In vitro	C23246
Drug transporter substrate and inhibition	HEK293 and MDCK cells	In vitro	19SPRWP4
UGT enzyme inhibition	Recombinant human UGT isozymes	In vitro	C23255

Absorption

PK parameters of mirdametinib and its major metabolite, PD-0315209 were determined in dedicated studies following oral and IV administration of mirdametinib to male Sprague-Dawley rats, male and female beagle dogs, and male cynomolgus monkeys.

Intestinal absorption of mirdametinib is predicted to be high in the Caco-2 cell monolayer model. The solubility of the API was about 0.2 mg/mL at different pH buffers.

Following IV administration, mean plasma clearance (CL) values of mirdametinib were 3.28 (rat), 2.18 (dog), and 7.84 (monkey) mL/min/kg. Mirdametinib exhibited low plasma CL across the 3 non-clinical species evaluated. The mean apparent volume of distribution at steady-state (Vss) values for rats (1.18 L/kg) and monkeys (1.59 L/kg) were greater than the total body water (approximately 0.6 to 0.7 L/kg), while Vss in dogs (0.378 L/kg) was smaller than the total body water (Davis 1993). Both rats and monkeys exhibited moderate Vss, whereas dogs exhibited low Vss. Mean elimination half-life ($t_{1/2}$) values were 6.9 (rat), 3.5 (dog), and 6.0 (monkey) hours. The mean absolute oral bioavailability (F) of mirdametinib was moderate to high: 29.5% (rat), 103% (dog), and 43.7% (monkey). Following oral administration of a single dose of mirdametinib, the mean plasma AUC values for the metabolite PD-0315209 as a percent of parent were 32% (rat), 26% (dog), and 19% (monkey).

In rats and dogs, mean mirdametinib Cmax and AUC values increased in a dose-related manner over the dose range evaluated. Similar dose-related increases in plasma Cmax and AUC values were also observed for the metabolite PD-0315209. No meaningful sex-related differences in levels of mirdametinib or PD-0315209 were noted in mice and dogs. Female rats exhibited slightly lower overall exposures to mirdametinib, based on AUC0-24, across all dose groups and higher (4- to 5-fold) exposure to PD-0315209, based on both Cmax and AUC0-24; female rats metabolized mirdametinib to PD-0315209 to a greater extent than male rats.

Distribution

Mirdametinib showed high plasma protein binding (> 99%) in mice, rats, dogs, monkeys, and humans. The metabolite PD-0315209 also showed high plasma protein binding (> 99%) in humans. PD-0315209 has negligible participation in the biological activity of mirdametinib at the clinical dose. Its low clinical unbound Cmax based on studies NF 106 and MEK-NF-201 (1.6 nM) and the absence of protein binding investigation of PD-0315209 in repeat-dose toxicity studies in animals would not have an impact on the overall interpretation of the non-clinical assessment of mirdametinib. *In vitro* blood-to-plasma partitioning demonstrated preferential distribution of mirdametinib into plasma over whole blood in mice, rats, dogs, monkeys, and humans. A preferential distribution into human plasma over whole blood was also noticed.

A quantitative whole-body autoradiography (QWBA) study was conducted with [^{14}C]mirdametinib in male rats only. The radiolabelled C site is present in the parent and in the metabolite PD-0315209. For all tissues, the highest measured concentrations were observed within 4 hours and 0.5 hours post dose for the oral and IV routes, respectively. Drug equivalents were not retained in pigmented tissues (skin, retina). Distribution of [^{14}C]mirdametinib equivalents in the brain demonstrated distinct regional localisation with highest levels in the striatum, the hippocampus, and the olfactory bulb. The greatest tissue uptake after oral administration was seen in the liver, followed by the kidney, the blood, the adrenal, the lung, the salivary glands, the heart, and the pancreas. Tissue levels were below the limit of quantitation by 48 hours except for the liver and the brain (by 96h).

Recently, a dedicated study in rats after IV administration was performed to determine the brain's and the CSF's concentrations of mirdametinib and its metabolite. Mirdametinib and PD-0315209 entered in the rat's brain but in more limited extent for the metabolite PD-0315209. The half-life of mirdametinib in the rat's brain was longer than the half-life of mirdametinib in the plasma, therefore mirdametinib's brain to plasma ratio increased over time.

Metabolism

The metabolic profiles determined in vitro appear similar in humans', monkeys', dogs', and rats' hepatocytes and microsomes. Glucuronidation was the major metabolic pathway observed in humans', dogs', and monkeys' hepatocytes. A carboxylic acid metabolite of mirdametinib (PD-0315209) was detected in microsomal incubations without the addition of reduced nicotinamide adenine dinucleotide

phosphate (NADPH) as well as following preincubation with aminobenzotriazole, suggesting that this metabolite can be formed by non-CYP enzymes. The percent contribution to the synthesis of the primary metabolite was most significant for the UGT isoform 1A6 (57.9%). A reaction phenotyping assay explored the contribution of carboxylesterase (CES) on the metabolism of mirdametinib. The production of the metabolite PD-0315209 was highest with CES1b followed by CES1c, indicating that these enzymes may contribute to the conversion of mirdametinib to the primary metabolite PD-0315209.

Two mass balance studies were conducted by oral route administration of [^{14}C]mirdametinib in rats and dogs, the two species used for the toxicology studies. [^{14}C]mirdametinib underwent both glucuronidation (major) and oxidation (minor) of the parent compound. In the rat plasma, the major circulating drug-derived components consist of the parent (60% of radioactivity in males and 34% in females) and a carboxylic acid metabolite PD 0315209 (M 15) (21% and 57% of the radioactivity in male and female rats). Taken together, these 2 characterised components accounted for approximately 80% to 90% of the total circulating radioactivity. The majority of the drug related components were eliminated via biliary excretion. In dog plasma, the major circulating drug-derived components consist of the parent (79% of the radioactivity in males and 85% in females) and a carboxylic acid metabolite PD 0315209 (M 15) (18% and 15% of the radioactivity in male and female rats). Taken together, these 2 characterised components accounted for approximately 97% to 100% of the total circulating radioactivity.

In the human radiolabelled mass balance study (study MEK-NF-101), mirdametinib and the carboxylic acid metabolite PD-0315209 represented 35.3% and 24.0% of the total plasma radioactivity, respectively. Another metabolite of mirdametinib, M22 (a glucuronide metabolite), represented >10% of the total radioactivity in plasma (14.7% of the total plasma radioactivity). The mean combined total recovery of radioactivity over 264 hours post dose was 95.0%, with 67.7% recovered in the urine and 27.3% in the faeces. M22 glucuronide metabolite is either not present in the rat plasma (per M3) or present at a very low level in dogs (1.5% per M5) and was not measured in repeat-dose toxicology studies.

Excretion

Following oral administration of [^{14}C]mirdametinib to intact rats, the primary route of excretion of [^{14}C]mirdametinib equivalents was via the faeces (≥ 82%), with approximately 11% of the radioactivity dose recovered in the urine. In bile-duct cannulated rats, the total recovery in the bile was 85% and 70% for males and females, respectively. In intact dogs, approximately 95% and 89% were recovered in the faeces of male and female dogs, respectively, whereas the amount recovered in the urine accounted for approximately 2% for both male and female dogs.

DDI

No drug-drug interaction studies were conducted in animals. Please refer to section 2.6.2.1. Pharmacokinetics.

2.5.4. Toxicology

Mirdametinib was assessed in a non-clinical programme according to ICH M3 guideline. The oral route of exposure was selected for these studies as it is the intended clinical route of administration. The rat and dog were selected as the general toxicology species based on mirdametinib's PK and metabolism properties compared across species. Mitogen-activated protein kinase (MAPK) levels were measured in several different tissues in order to measure the PD activity in animal species: PD activity is confirmed in the 3 species used (rats, dogs and monkeys). The definitive studies were performed in accordance with the OECD principles of GLP. Administration in animals was conducted once daily while clinical

treatment is administrated twice daily. Several single dose studies were performed in rats and in monkeys. Then, 2-weeks dose range studies were performed in rats, dogs and monkeys. Pivotal studies were performed in rats and dogs up to 3 months. No chronic studies were performed. In the 3-month rat study, exposures above the clinical exposure were reached at the high dose. Clinical experience with mirdametinib and its metabolite PD 0315209 is currently sufficient to waive the need for long-term animal studies. A standard battery for genotoxicity testing was performed and an additional *in vivo* test was conducted to investigate the equivocal results from the first *in vivo* study. A 26-week carcinogenicity study in mice was performed after a dose range study and a 2-year carcinogenicity study in rats is currently ongoing (started in August 2024). Preliminary embryo-foetal development (pEFD) toxicity studies were conducted in rats and rabbits. No definitive EFD studies were conducted. A fertility study was conducted in male and female rats. Juvenile animal studies were not conducted. The phototoxic potential was determined *in vitro* in 3T3NRU and a 1-month study was performed to qualify impurities (S-enantiomer).

Mirdametinib batches used in non-clinical safety studies

The test article used in the non-clinical studies was representative of the drug substance used in the clinic and that of the commercial drug product.

2.5.4.1. Single dose toxicity

In both species (rat and monkey), the main observed acute toxic effects were effects on the gastrointestinal (GI) tract.

In the rat, mirdametinib was lethal at high doses (≥300 mg/kg). The human equivalent dose (HED) based on a body surface area (BSA) of 300 mg/kg is 49 mg/kg for an adult human (2919 mg for an adult of 60 kg), and 72 mg/kg for a child (1440 mg for a child of 20 kg).

In the monkey, the maximum non-lethal oral dose was 10 mg/kg, associated with an AUC_{0-24} of 8745 ng.h/ml for mirdametinib (4.7-fold the mean steady-state clinical exposure) and AUC_{0-24} of 1865 ng.h/ml for metabolite PD-315209 (1.4-fold the mean steady-state clinical exposure).

2.5.4.2. Repeat dose toxicity

Mice

The repeat dose toxicity of mirdametinib was evaluated in mice. A 5-day (doses from 25 to 225 mg/kg/day) and 28-day (doses from 10 to 100 mg/kg/day) range-finding study by oral gavage in CByB6F1 hybrid mice (Tg.rasH2 non-transgenic littermates) was conducted to establish the dose levels for the 6-month definitive Tg.rasH2 carcinogenicity study. All evaluated mirdametinib dose levels were associated with mirdametinib AUC exposures well above (≥5-fold) the clinical exposures. Mortality occurred at 225 mg/kg/day in the 5-day phase and at 100 mg/kg/day in the 28-day phase of the study. A NOAEL could not be determined. The main toxicities were found in the GI tract (inflammatory cell infiltrates, epithelial degeneration/necrosis, erosion/ulceration, epithelial hyperplasia), liver (increases in liver enzymes, hepatocellular necrosis), testis (degeneration/necrosis), adrenal gland (cortical degeneration/necrosis) and lymphoid organs (reduced cellularity in the thymus, bone marrow and mesenteric lymph nodes).

Rat

A dose range finding study was performed. Mirdametinib was administrated for 14 days at 3, 10 and 30 mg/kg/day. Mortality was observed in males at all doses and in females at 10 and 30 mg/kg/day. The lethal dose in the 2-week dose-range finding study is much lower than the lethal dose in the single oral dose toxicity study in rats, suggesting that mirdametinib produces toxicity in a cumulative fashion,

depending on the dose and the length of administration. Mineralisation in multiple soft tissues skin ulceration, hepatocellular necrosis, decreased goblet cells in the colonic crypts (GI tract), and femoral metaphysis degeneration/necrosis were observed. Hepatocellular necrosis was observed in the 2-week study but not in the longer 1-month and 3-month repeat-dose toxicity studies in rats (only increases in liver enzymes). A more pronounced toxicity was observed in males than in females despite similar exposure to the parent and greater exposure to the metabolite PD0315209 in female rats. No NOAEL or MTD was determined in this study, the minimal lethal dose was determined at 3 mg/kg/day (2.7-fold the clinical exposure at the intended dose).

A one-month GLP study was conducted in rats. Mirdametinib was administrated for 4 weeks at doses of 0.1, 0.3 and 1 mg/kg/day. Only rat exposures at the highest dose were demonstrated to be in the range of the clinical exposure at the intended recommended dose (as per the indication). The exposures at low and mid dose are below the clinical range exposure. A recovery period of 4 weeks was added. The toxicity observed in this study is more pronounced in males than in females. Vascular and soft tissue mineralisation (systemic mineralisation) was the most toxicologically relevant change observed and is consistent with the 2-week dose range finding study in rats. Systemic mineralisation was not reversible after a recovery period. Skin lesions were observed clinically at dose of 0.1 mg/kg and above and were characterised by epidermal ulceration, which appear reversible after a 4-week recovery. Finally, reversible hypocellularity in bone marrow was also observed and was more pronounced in males than in females. The determined NOAEL was 0.1 mg/kg/day in male rats and 0.3 mg/kg/day in female rats. Exposures at these doses are below the clinical predicted exposure at the intended posology.

The three-month GLP study was conducted in rats. Mirdametinib was administrated for 13 weeks at dose of 0.1, 0.3 and 1 mg/kg/day (same doses used in the 4-weeks study). Only rat exposures at the highest dose were demonstrated to be in the range of the clinical exposure at the intended recommended dose (as per the indication). The exposures at low and mid dose are below the clinical range exposure. No recovery period was added. The primary drug-related toxicities were systemic mineralisation, corneal opacities, skin ulcers or crusts, changes in female reproductive tract, dysplasia in epiphyseal growth plate, thickening of the bone trabeculae and metaphyseal hypocellularity of the bone marrow. Overall, males were more sensitive than females despite similar exposure to mirdametinib. As observed in the 1-month study, systemic mineralisation was accompanied by elevated phosphorus (hyperphosphatemia) and decreased albumin with unchanged calcium values. New findings not observed in the previous 1-month oral toxicity study were corneal opacities, changes in female reproductive tract and dysplasia in the epiphyseal growth plate. Focal corneal opacities were observed at all dose levels, in a dose-dependent manner, mainly in males. Skin lesions were observed clinically at the end of the study at high dose only and were correlated macroscopically with wounds/scars/scabs and microscopically with epidermal ulcers and crusts. There was an increased proportion of females staged in dioestrus (9/10 females) at 1 mg/kg/day and the ovaries of several females (6/10) had increased numbers of follicular cysts associated with a reduction in the number of corpora lutea. This correlated with decreased ovarian weights. Bone effects comprised dysplasia in the femoral epiphyseal growth plate and metaphyseal hypocellularity of the bone marrow of long bones from 0.3 mg/kg/day, and metaphyseal thickening of the bone trabeculae of long bones at 1 mg/kg/day. The lowest dose was determined as the LOAEL and the rat exposures were far lower than the clinical exposure predicted at the intended posology.

To conclude, studies in rats up to 3 months identified severe toxicity findings at exposures lower than the clinical exposure predicted at the intended clinical posology. The observed toxicity profile was consistent through non-pivotal and pivotal rat studies. The primary drug-related toxicities were systemic mineralisation, corneal opacities, skin ulcers or crusts, changes in female reproductive tract, dysplasia in epiphyseal growth plate, thickening of the bone trabeculae and metaphyseal

hypocellularity of the bone marrow. Males appeared more sensitive to all toxic findings observed than female despite similar exposures, and the mechanism behind such observation is unknown. The systemic mineralisation, eye findings and bone effects are discussed in further detail below.

Systemic mineralisation

Systemic mineralisation was observed in all repeat-dose toxicity studies in rats. The incidence of this finding is much higher in males than females. The stomach appears to be the most sensitive tissue since mineralisation of gastric fundic mucosa occurs prior to the onset of mineralisation in other tissues.

In the 2-week dose-range finding study, staining for calcium was conducted which indicated the presence of calcium in the mineralised lesions. The systemic mineralisation may be related to dysregulation of the serum calcium and phosphorus homeostasis in rats treated with mirdametinib. Elevated phosphorus and decreased albumin with unchanged calcium values were observed in rats given mirdametinib. As mentioned in Diaz et al. (2012), decreases in albumin levels could result in an underestimation of the level of free calcium and thus potentially mask an increase in calcium.

Systemic mineralisation was only observed in rats and not in the other tested species (dog, monkey, mouse).

Eye findings

Eye findings were only observed in rats and included focal corneal opacities, mineralisation in the basement membrane of corneal epithelium and atrophy or thinning of the corneal epithelium.

According to the study report of the 3-months repeat-dose toxicity study in rats, corneal opacities were a new finding not observed in the previous 1-month oral toxicity study.

Bone effects

The bone and bone marrow changes were reversible in the 1-month study. However, in the 3-months study there was a new finding (dysplasia in epiphyseal growth plate) of which the reversibility is unknown since reversibility was not assessed in the 3-months study.

Dog

Preliminary studies were conducted as dose escalation in a limited number of dogs (1/sex) by IV or oral dose administration. A 2-weeks dose range finding study was also conducted. These three studies identified dose-limiting toxicities with deaths occurring at ≥ 0.5 mg/kg due to GI toxicities (epithelial necrosis, ulceration, and erosion). The maximum tolerated dose was 0.2 mg/kg/day (0.7-fold the clinical exposure predicted at the intended posology). Systemic mineralisation was not observed in the dog range-finding studies. To be noticed, the kidney was a target organ in the IV escalation-dose toxicity study in the dog but not in any other repeat-dose toxicity study in dogs. Hepatotoxicity (hepatocellular swelling, increased neutrophils in hepatic sinusoids and single cell necrosis of hepatocytes) was observed in the oral escalation study at exposures well above the clinical exposure at the intended doses. Based on the outcome of the range-finding studies, the dose levels for the 1-month dog study were selected to be 0 (vehicle), 0.05, 0.1, or 0.3 mg/kg/day administered once daily by oral gavage.

A one-month GLP study was conducted in dogs. Mirdametinib was administrated for 4 weeks at doses of 0.05, 0.1, or 0.3 mg/kg/day. Dog exposures at the highest dose were a little less than the clinical exposure predicted at the intended recommended dose (as per the indication). The exposures at low and mid dose are far below the clinical range exposure (0.12- and 0.35-fold respectively). A recovery period of 4 weeks was added. The skin appeared to be the primary target for drug-related toxicity in this study. Skin sores were observed in 2 animals at the highest dose, one of the lesions was

characterised by focal epidermal ulcer with neutrophilic inflammation with surface crusts (bacterial colonies). This finding was not observed at the recovery necropsies. Minor changes in red blood cell parameters were observed also in the high dose group which were also reversible. Hypoactivity was observed periodically during the dosing period in the high dose group (3 males/4 and 2 females/4 at 0.3 mg/kg/day) although no severe toxicity was observed at this dose. Dose dependent increases of serum phosphorus levels occurred in dogs with a rise in plasma 1,25-dihydroxyvitamin D in males (no change in serum calcium level). However, systemic mineralisation was not observed. The study report indicated that this variation was of insufficient magnitude to result in potential toxicity. PD activity was checked by measurements of lung and colon pMAPK levels. There was a high degree of variability, statistically significant changes were not observed. Biological inhibition of pMAPK was more evident in the colon than in the lung. The NOAEL was identified at 0.1 mg/kg/day (0.35-fold the clinical exposure).

The three-months GLP study was conducted in dogs. Mirdametinib was administrated for 13 weeks at dose of 0.05, 0.1 and 0.4 mg/kg/day. The number of animals (n = 3/sex/group) in this study was lower than the recommended number of non-rodents according to the OECD test guidelines (n = 4/sex/group). Only dog exposures at the highest dose at D41 were demonstrated to be in the range of the clinical exposure at the intended recommended dose (as per the indication). The exposures at low and mid dose are far below the clinical range exposure. No recovery period was added. At the dose of 0.4 mg/kg/day, after D33, the treatment induced moribundity in 4/6 animals following a range of severe clinical effects. The cause of moribundity was not apparent grossly or microscopically. These moribund dogs presented CNS effects (decreased activity, tremors, titubation (a staggering or stumbling gait), impaired balance, arched back with rigid/extended limbs, and stiff neck). These CNS effects were not observed in the 2 surviving animals and were without microscopic correlates.

Monkey

A 2-weeks study was performed to determine if soft-tissue mineralisation occurs in this species. Mirdametinib was administrated in cynomolgus monkeys at 0.5, 3 and 10 mg/kg/day once daily for 14 days. Mirdametinib was not tolerated at 10 mg/kg/day with some morbidity observed due to GI injury. A no-adverse-effect dose was not identified as clinical signs and GI tract changes were seen at ≥ 0.5 mg/kg/day (0.14-fold the clinical exposure). No calcium-phosphorus homeostasis alterations and no evidence of systemic mineralisation were observed. The gallbladder and the skin were also affected but only in the high dose group (3.7-fold the clinical exposure). Therefore, this monkey study identified a new target organ for mirdametinib (gallbladder) that was not identified in other non-clinical species. The gallbladder toxicity (gross changes including abnormal colour or abnormal content, microscopically transmural necrosis) occurred at 10 mg/kg/day associated with day 1 mirdametinib AUC0-24 exposures ranging from 4790 – 15000 ng*h/ml, i.e. >2.5-fold above clinical exposure.

Hepatic effects:

Hepatic effects were noted in several repeat-dose toxicity studies in several species:

- Increases in liver enzymes occurred in the 1-month and 3-months repeat-dose toxicity studies in rats at exposures below/similar to the clinical exposure. In the clinical studies in NF1 PN patients, increased liver enzymes (AST, ALT) have also been observed.

- Microscopic findings in the liver were observed in some repeat-dose toxicity studies. Hepatocellular necrosis was observed in the 28-day toxicity study in mice at all dose levels tested (at lowest dose only in males, associated with exposures 8.8-fold clinical exposure). Multifocal, coagulative, hepatocellular necrosis occurred in the 2-weeks study in rats in males at ≥ 3 mg/kg/day (lowest dose evaluated; 2.5x exposure multiple) and in females at ≥10 mg/kg/day (exposure multiple of ±26x). In the oral escalation dose study in dogs, hepatocellular swelling and increased neutrophils

in hepatic sinusoids was observed in the original male and female as well as single cell necrosis of hepatocytes in the original male (mirdametinib AUC0-24 was 20-fold the human exposure). Hepatocellular vacuolation and necrosis were observed in the 26-weeks carcinogenicity study in transgenic mice at ≥2 mg/kg/day (exposure multiple ≥1.2x).

2.5.4.3. Genotoxicity

Genotoxicity testing of mirdametinib was performed in line with ICH S2(R1) and OECD testing guidelines (471, 473, 474, 475). The number of cells analysed in the *in vitro* and *in vivo* chromosome aberration assays was lower than what is mentioned in the current OECD testing guidelines. However, the studies were conducted in line with the testing guidelines effective at the time of study conduct.

Rat liver S9 was used as metabolic activation system in the in vitro studies and the *in vivo* studies were conducted in rats.

Mirdametinib was negative in the bacterial reverse mutation assay and in the *in vitro* chromosome aberration assay in human lymphocytes.

In the *in vivo* studies, doses up to 3 mg/kg/day were evaluated. The selection of the dose levels was based on the 2-week oral dose-range finding study in rats (study 745-03478) and on an exploratory 4-day oral toxicity study in male rats. 10 mg/kg/day did not cause mortality in the 4-day exploratory rat study (study 745-03732) and only resulted in mortality from day 6 onwards in the 2-week rat study (745-03478).

TK analyses were not performed in the *in vivo* genotoxicity studies. In the 2-week DRF study in rats (study 745-03478), the mean sex-combined day 1 mirdametinib AUC0-24 was 5580 ng.h/ml at 3 mg/kg (exposure multiple ±3x) and the mean PD-0315209 (metabolite) exposure was 2210 ng.h/ml in males (exposure multiple 1.6x) and 10400 ng.h/ml in females (exposure multiple 10x). As such, it can be assumed that the animals in the *in vivo* genotoxicity studies have been exposed to mirdametinib and the metabolite PD-0315209 exposures that exceed the clinical exposures (±3-fold for mirdametinib).

According to the applicant, mirdametinib was negative in the *in vivo* micronucleus assay and a battery of genotoxicity studies.

2.5.4.4. Carcinogenicity

The carcinogenic potential of mirdametinib was assessed in a 6-month study in transgenic rasH2 mice. The dose levels established for this study (0, 2, 5, 15 mg/kg/day) were selected on the MTD of 10 mg/kg/day determined in the 28-day DRF study in transgenic mice. No carcinogenic effect was observed in this study up to 5 mg/kg/day (3.6-fold the clinical exposure predicted at the intended posology). Indeed, female Tg mice dosed at 15 mg/kg/day presented an insufficient survival (only 16% at week 24) to consider the carcinogenic assessment relevant in this group. Therefore, only the absence of an effect up to a dose level of 5 mg/kg/day is considered.

A 2-year carcinogenicity has started in August 2024. Rats will be treated at dose levels of 0.03, 0.1 and 0.3 mg/kg/day. Based on the observed 3-month exposure in rats, exposure observed in rats treated at 0.3 mg/kg/day mirdametinib were below the clinical exposure range (0.58-fold).

2.5.4.5. Reproductive and developmental toxicity

In the fertility study conducted at doses ranging from 0.1 to 1 mg/kg/day, treatment-related skin lesions were observed macroscopically in high dosed male animals in line with results from the general toxicity studies at similar dose levels. Treatment with mirdametinib did not cause any significant

adverse effect on mating and fertility parameters, and early embryonic development. Therefore, the NOAEL for male and female reproductive toxicity and early embryonic development in this study was 1 mg/kg/day. However, findings in reproductive organs were observed in several repeat-dose toxicity studies. In the 28-day mouse study, decreased ovary weights and increased uterus weights were reported at 10 mg/kg/day and 30 mg/kg/day, and testicular degeneration/necrosis was seen at all tested dose levels (≥10 mg/kg/day); the study report mentions that this testicular finding is likely due to stress and/or mirdametinib-related clinical decline, although a direct effect of mirdametinib cannot be ruled out. This finding was not seen in the 26-week carcinogenicity study in transgenic mice at doses up to 15 mg/kg/day. In rats dosed for 1 month, decreased weights of ovaries was observed at ≥0.3 mg/kg/day (exposures below or at clinical exposure) without microscopic correlate. In the 3-month study, there was an increased proportion of females (9/10) in dioestrus at 1 mg/kg/day and decreased ovarian weights at all doses without microscopic correlate. Ovaries of 6/10 females at 1 mg/kg had increased number of follicular cysts associated with a reduction in the number of corpora lutea.

Dose-range finding embryo-foetal development studies were conducted in rats and rabbits at dose levels ranging from 0.3 to 6 mg/kg/day. In the rat study, the doses ranged from 0.25 to 5.05 mg/kg/day based on results of formulation concentration assays. Maternal toxicity was observed at 5.05 mg/kg/day as evidenced by clinical signs (skin-related findings) and decreases in body weight gain, body weight, and food consumption. Treatment-related embryo-foetal lethality was reported from the non-maternotoxic dose of 0.64 mg/kg/day based on an increase in group mean value for early resorptions at ≥3.0 mg/kg/day and death of one rat at 0.64 mg/kg/day caused by treatment-induced late resorptions (no live foetuses) and related red fluid within the uterus. In addition, various external malformations affecting the extremities (limbs, digits, and tail) were reported in one foetus in the group dosed at 3.0 mg/kg/day; this finding was considered as treatment-related considering the developmental toxicity profile of MEK inhibitors. Moreover, foetal body weight was also decreased at ≥ 0.64 mg/kg/day. Therefore, the NOAEL for developmental toxicity in rats was of 0.25 mg/kg/day. In rabbits, maternal toxicity was observed at 1 mg/kg/day based on abortions, body weight loss, decreased food consumption, decreased urine and faecal output, and stomach ulceration. At ≥3 mg/kg/day, effects were more marked leading to unscheduled termination of all animals on GD 15/16. Ovarian and uterine examination of animals surviving to C-section on GD29 in groups dosed at 0.3 and 1 mg/kg/day showed treatment-related increases in early and late resorptions, with a correlating decrease in the number of live foetuses. In addition, foetal weight was decreased at 1 mg/kg/day.

Definitive embryofoetal development and pre- and postnatal development studies were not conducted with mirdametinib.

A marketing authorisation is currently sought for patients aged 2 years and older. No juvenile animal study (JAS) was conducted with mirdametinib.

2.5.4.6. Toxicokinetic data

Please refer to section 2.5.4.2. Repeat dose toxicity for margins of exposure reported in the repeat dose toxicity studies.

2.5.4.7. Local tolerance

No dedicated local tolerance studies were conducted.

2.5.4.8. Other toxicity studies

Metabolite PD-0315209

Although initially presented as 24% exposure of the parent mirdametinib (clinical mass balance study), the exposure in patients for the metabolite PD-0315209 at steady state is predicted to be similar to the parent. The popPK report presented a mean steady-state AUC_{0-24} of 1862 ng·h/mL at 2mg/m^2 BID with a maximum of 4 mg BID for mirdametinib and a mean steady-state AUC_{0-24} of 1362 ng·h/mL for metabolite PD 0315209 when mirdametinib is administered at 2mg/m^2 BID with a maximum of 4 mg BID. PD-0315209 was found to be significantly less potent than the parent mirdametinib, with a range of IC50 values from 5291 to >10000 nM for PD-0315209 compared with 1.2 to 4.3 nM for mirdametinib across cell lines and incubations times. Overall the pharmacological activity of PD 0315209 is considered negligible at the clinical dose of mirdametinib. No secondary PD screening assay was performed with the metabolite PD-0315209.

A dedicated hERG study was performed with the metabolite PD-0315209. PD-0315209 was measured in repeated dose toxicity studies conducted with mirdametinib. PD-0315209 could be considered characterised in rats and transgenic mouse studies. However, PD-0315209's exposure is too limited in dogs to be considered characterised. No dedicated genotoxicity studies with PD-0315209 were performed. PD-0315209 was predicted negative for mutagenicity in two complimentary in silico systems. In *in vivo* genotoxicity studies, no PK analysis was performed but assumptions made from the repeated dose toxicity in rats indicated that PD-0315209 is between 1.6-10 at the high dose used in these studies.

S-enantiomer (PD-0326116)

Mirdametinib has 1 chiral centre. Mirdametinib is the R optical isomer, PD-0326116 is the S-isomer. The PD-0326116 enantiomer impurity is specified in the mirdametinib drug substance with a limit of NMT 0.50% area to ensure the quality of the drug substance and this impurity has been qualified up to 0.6% area in non-clinical safety studies. PD-0326116 has been qualified to a level of 0.62% area in development batches. Indeed, mirdametinib batch XH451101, used in the pivotal 1-month and 3-month GLP rat and dog studies and in the *in vivo* genotoxicity studies in rat, contained 0.62% area PD-0326116.

The IC_{50} of PD-0326116 is 0.82 nM in C26 cells, >2-fold lower than that of mirdametinib (IC50=0.33 nM). S-enantiomer clinical exposure is at a minimum of 11-fold and on average between 49- and 65-fold lower than mirdametinib exposure (based on Cmax).

Phototoxicity

An *in vitro* test (3T3 NRU) was performed given mirdametinib absorbs light in the 290-700nm range. However, no molar extinction coefficient (MEC) value was mentioned. The results of the *in vitro* prediction demonstrated an equivocal phototoxicity response (PIF ≥ 2 and <5). The applicant argued that distribution study demonstrated mirdametinib was not retained in the skin or eye based on the ^{14}C rat study which is agreed. Therefore, the applicant considered the human risk could be considered low.

2.5.5. Ecotoxicity/environmental risk assessment

Table 5: Summary of main study results

Substance (INN/Invented Name): mirdametinib			
CAS-number (if available): 391210-10-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH5: LogPow=3.1 pH7: LogPow=3.0 pH9: Log Dow=2.1	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{sw,\ refined}$	0.00045	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)	None		

2.5.6. Discussion on non-clinical aspects

The non-clinical programme for mirdametinib was performed according to ICH M3. Rats and dogs were used as relevant species based on PK and metabolism data. The applicant did not discuss the pharmacological relevance of the two animal species tested in pivotal studies.

Pharmacology

Mirdametinib is an inhibitor of MEK1 and MEK2. IC_{50} values based on *in vitro* results, which are determined to be around 0.33 nM whole cell (Colon 26 assay), are well within the clinically relevant concentrations.

The proof-of-concept is based on two recent literature references (Jessen et al. 2013[6],Jousma et al. 2015[7]). Mirdametinib was administrated to a genetically engineered mouse model of the NF1 neurofibroma disease (Nf1fl/fl;Dhh-Cre mouse model). Tumour volume and cell proliferation biomarkers were reduced; however, the most efficacious levels could not be determined as the three dose levels resulted in similar response amplitudes. The proof-of-concept in this genetically modified mouse model could be considered sufficient to support the intended indication. The participation of the metabolite PD-0315209 (carboxylic acid) and PD-0326116 (the S-enantiomer) in the overall PD activity has been discussed and appears limited or negligible.

No secondary PD screening assay was performed with the metabolite PD-0315209. However, metabolite PD-0315203 could be considered characterised in repeated dose toxicity studies in rats and given its structure, it could be assumed that off-target potential effects could be covered by these studies.

No study has been performed although a concern was raised on calcium channel in secondary PD screening assay. The applicant is asked to investigate potential effect of mirdametinib and its metabolite on Na/Ca channel (see section 2.6.3 Discussion on clinical pharmacology) considering the decreases of ejection fraction observed in humans. Considering that the sequences and structures of MEK1 and MEK2 are highly homologous across species, and similar metabolic profiles observed between humans and monkeys, monkeys may be considered as relevant animal species.

The applicant's rationale that decreased locomotor activity at 100 mg/kg could not be differentiated between general toxicity and CNS effects is not accepted since clinical signs seen during cage-side observations did not suggest any severe toxicity as well as the observations at higher exposure in the

[6] Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J Clin Invest. 2013;123(1):340-347. doi: 10.1172/JCI60578.
[7] Jousma E, Rizvi TA, Wu J, et al. Preclinical assessments of the MEK inhibitor PD-0325901 in a mouse model of Neurofibromatosis type 1. Pediatr Blood Cancer. 2015;62(10):1709-1716. doi: 10.1002/pbc.25546.

second study (one single IV dose up to 150 mg/kg). Therefore, effects on locomotor function were observed at 100 mg/kg and could be related to mirdametinib's administration; this toxic effect is largely above the clinical exposure at the intended clinical dose of 2mg/m^2 (>100-fold). Effects on the CNS were observed in dogs after repeated dose administration (see section 2.5.4).

Overall, non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology. The pharmacology package is considered adequate.

Pharmacokinetics

PK parameters of mirdametinib and its major metabolite, PD-0315209, were determined in dedicated studies following oral and IV administration of mirdametinib to male Sprague-Dawley rats, male and female beagle dogs, and male cynomolgus monkeys and TK parameters were followed in repeat dose toxicity studies. Unfortunately, no TK measurements were added in the *in vivo* genotoxicity studies. Mean elimination half-life values were 6.9 (rat), 3.5 (dog), and 6.0 (monkey) hours. These relatively short half-lives could have supported an administration twice daily in animals while in humans, the mass balance study demonstrated a half-life of 28h. As highlighted in the PD part, the difference in terms of efficacy after administration QD vs BID was not studied. In rats and dogs, mean mirdametinib and PD-0315209 C_{max} and AUC values increased in a dose-related manner over the dose range evaluated. No sex differences in the levels of mirdametinib or PD-0315209 were noted in mice and dogs. Female rats exhibited slightly lower overall exposures of mirdametinib, based on $AUC_{0\text{-}24,}$ across all dose groups and higher (4- to 5-fold) exposure of PD-0315209. Mirdametinib showed high plasma protein binding in all species. PD-0315209 was not tested in animal species, only in humans (see section 2.6.2.1 Clinical PK).

A QWBA study was conducted with [^{14}C]mirdametinib in male rats only. For all tissues, the highest measured concentrations were observed within 4 hours and 0.5 hours post dose for the oral and IV routes, no specific retention was observed in melanin-containing tissues. The greatest tissue uptake after oral administration was seen in the liver, followed by the kidney, blood, adrenal, lung, salivary, heart, and pancreas. Tissue levels were below the limit of quantitation by 48 hours except for the liver and brain (by 96h). A study to determine the brain and CSF concentrations of mirdametinib and its metabolite in dogs would have been preferred to the additional study conducted in rats.

Glucuronidation was the major metabolic pathway in human, dog, and monkey hepatocytes. A carboxylic acid metabolite of mirdametinib (PD-0315209) was detected *in vitro* and *in vivo*. The metabolite PD-0315209 was present in rats, dogs and monkeys. The metabolite M22 is either not present in rat plasma (per M3) or present at a very low level in dogs (1.5% per M5) and was not measured in repeat-dose toxicology studies given that it is an inactive O-glucuronide conjugate. M22 is derived from Phase 2 conjugation reactions and generally renders a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation.

Following oral administration of mirdametinib to rats and dogs, the primary route of excretion of mirdametinib equivalents was via the faeces as opposed to urine in humans (see section 2.6.2. Clinical pharmacology).

The pharmacokinetic package is considered adequate.

Toxicology

The non-clinical programme conducted according to ICH M3 recommendations could be considered sufficient as clinical experience with mirdametinib and its metabolite PD 0315209 is demonstrated to be sufficient to waive the need for long-term animal studies. Animals were treated once daily by oral route while patients received the treatment twice daily. Primary treatment-related toxicities were attributed to the pharmacological activity of mirdametinib in GI tract, skin, liver, systemic

mineralisation, gallbladder and bone and were already identified for molecules which present this mechanism of action. Male rats appeared more sensitive to all toxic observed findings compared to female rats despite similar exposures, the mechanism is not known. These toxicities were observed at far lower exposures than the clinical exposure range at the intended exposure.

Systemic mineralisation was observed in rats and not in the other tested species (dog, monkey, mouse). The clinical relevance of this toxic finding is not known. The rat studies supported the mechanism of systemic mineralisation related to dysregulation of serum phosphorus and calcium homeostasis via elevations in plasma 1,25-dihydroxyvitamin D following mirdametinib administration. It is not clear whether systemic mineralisation could occur/occurs in humans treated with mirdametinib. The human relevance of this finding is unknown.

Soft tissue mineralisation has also been observed with several other MEK1/2 inhibitors in rodents, namely selumetinib, trametinib and binimetinib (in the EPAR and potentially also in the SmPC).

Systemic mineralisation in the rat repeat-dose toxicity studies is reported in the RMP and section 5.3 of the SmPC.

In relation to eye toxicities, in the 1-month repeat-dose toxicity study in rats, there were some findings in the ophthalmologic examinations of mirdametinib-treated animals during week 4 (roughness cornea, ulceration cornea and focal corneal opacity) and during week 8/recovery (retinopathy in one male in the 1 mg/kg group) and there were microscopic findings of mineralisation in the conjunctiva in 3 animals at 1 mg/kg/day and inflammation of the anterior chamber in 1 animal at 1 mg/kg/day. In the 3-months repeat-dose toxicity there were also findings of corneal opacities.

The mechanism of eye toxicities observed in rats (corneal opacities) is not fully identified. It was suggested that tissue mineral deposition mediated by elevations in plasma 1,25-dihydroxyvitamin D levels could be the cause for the corneal opacities in rats. However, corneal opacities occurred already at lower doses while mineralisation in cornea/conjunctiva was only observed at 1 mg/kg/day and elevations in 1,25-dihydroxyvitamin D levels were not seen in the 1-month rat study (not measured in 3-month study). This proposed mechanism is thus questionable.

The observed thinning or atrophy of the corneal epithelium at ≥0.3 mg/kg/day in the 3-month study may be secondary to effects on cell/keratinocyte turnover as a reflection of the pharmacology (cytostatic nature) of the compound. Corneal thinning is likely reversible following drug withdrawal.

Ocular toxicities have been reported in humans treated with mirdametinib. However, the ocular toxicities observed in humans (retinal vein occlusion, retinal pigment epithelium detachment) are different from the ones observed in the rats (see section 2.6.9 Clinical safety).

Of note, ophthalmology findings were also noted for selumetinib, i.e. oval opacities across cornea and rough appearance to cornea in mice treated with selumetinib (mentioned in the EPAR but not in SmPC).

Ocular toxicity is a class effect for MEK inhibitors and patients are monitored for eye toxicity and a dose adjustment is proposed in section 4.2 in case of retina findings. Eye toxicity is reported in RMP and SmPC section 5.3. Ocular findings (corneal opacities and atrophy or thinning of the corneal epithelium) observed in the rat studies are reflected in section 5.3 of the SmPC, and in the RMP).

The bone and bone marrow changes were reversible in the 1-month study with mirdametinib. However, in the 3-month study there was a new finding (dysplasia in epiphyseal growth plate) of which the reversibility is unknown since reversibility was not assessed in the 3-month study. It is reported in section 5.3 of the SmPC that reversibility of dysplasia in epiphyseal growth plate was not evaluated.

Bone effects were also noted in rats for other MEK inhibitors: growth plate (physeal) dysplasia was seen in male rats dosed for up to 3 months with selumetinib at a free exposure 11 times the clinical free exposure at the maximum recommended human dose (MRHD) (see SmPC and EPAR of Koselugo). With trametinib, hypertrophy of the physis and increased bone turnover were observed in rats (see SmPC of Mekinist).

The human relevance of the bone effects observed in rats is not clear. The risk of physeal dysplasia was added in the RMP as an important potential risk (Diaz D et al, 2012).

CNS effects were observed in the 3-month pivotal dog study in 4 high-dose dogs at 0.4 mg/kg/day with exposures approximately 1.4× that observed in humans. No CNS toxicity was identified with the other MEK inhibitors. The observed CNS toxicity with mirdametinib is however consistent with the rat distribution study. CNS effects were also identified in clinical trials; two patients receiving 15 mg BID experienced transient visual hallucinations possibly related to mirdametinib. This suggests that the CNS is a target organ of toxicity for mirdametinib or at least a cause of concern. The CNS is a potential target for human effects, and it is reported in the RMP and in the SmPC section 5.3.

A monkey study identified a new target organ for mirdametinib (gallbladder) that was not identified in other non-clinical species. The gallbladder toxicity (gross changes including abnormal colour or abnormal content, microscopically transmural necrosis) occurred at 10 mg/kg/day associated with day 1 mirdametinib AUC0-24 exposures ranging from 4790 – 15000 ng*h/ml, i.e. >2.5-fold above clinical exposure (see SmPC section 5.3).

Liver toxicity (increases in liver enzymes in rats at exposures below/similar to clinical exposure and hepatocellular necrosis in mice, rats and dogs at exposures similar/above clinical exposure) is reported in SmPC section 5.3. Hepatic effects are reported in table 3 of the RMP and in the SmPC section 5.3.

Mirdametinib was not mutagenic in bacteria and was not clastogenic in human lymphocytes *in vitro*. The selection of 3 mg/kg/day as the high dose for the *in vivo* genotoxicity studies is questioned because a higher dose (i.e. 10 mg/kg/day) would probably also have been feasible/tolerated for a treatment period of 2 days. TK analyses were not performed in the *in vivo* genotoxicity studies. This is considered acceptable and in line with ICH S2(R1) given that *in vivo* systemic exposure can be assumed from the results of other *in vivo* studies that have been conducted in rats with mirdametinib. In the *in vivo* micronucleus test, mirdametinib was not genotoxic to the bone marrow of rats at doses up to 1 mg/kg (exposure clinical range). At 3 mg/kg a statistically significant increase in micronucleated polychromatic erythrocyte (MNPCE) formation was observed in females, suggesting that mirdametinib may have genotoxic potential (around only 3-fold-fold the clinical exposure). An additional study, i.e. an *in vivo* chromosome aberration study in rats was conducted, for which also an equivocal response was obtained. The overall conclusion that mirdametinib was negative in a battery of genotoxicity studies is currently not agreed. Both *in vivo* genotoxicity studies are considered equivocal. The genotoxicity risk for treated patients could not be excluded at the clinical exposure range. Additional studies in mice will be performed post-approval to further characterize the genotoxicity risk and to determine the mechanism effect (REC).

The 26-week carcinogenicity study of mirdametinib in Tg RasH2 mice was negative up to 5 mg/kg/day (3-fold (M)/4.2-fold(F) the clinical exposure and the mean metabolite PD-0315209 AUC exposure 0.5-fold (M)/1.2-fold(F) the clinical exposure). The ongoing 2-year carcinogenicity study in rats is performed at dose levels of 0.03, 0.1 and 0.3 mg/kg/day. Exposures observed in rats treated at 0.3 mg/kg/day mirdametinib are below the clinical exposure range (±0.58-fold). Therefore, the added value of the 2-year rat study is questionable, and a genotoxicity risk at the clinical range could not be discarded. Carcinogenicity has been added in the RMP as 'important potential risk' and as previously mentioned additional genotoxicity studies in mice will be performed post-approval to further

characterize the carcinogenicity risk (REC). A potential carcinogenicity risk in humans could not be excluded at the clinical exposure range as reflected in section 4.4 of the SmPC.

In developmental and reproductive toxicity studies, mirdametinib did not cause significant adverse effect on mating, fertility, and early embryonic development at doses up to 1 mg/kg/day. No safety margin could be derived since this high dose level corresponds to exposure levels within the clinical range (x1.1-2.1). In parallel, findings on reproductive organs were observed in some toxicity studies (e.g. 28-day and 26-week studies in transgenic mice, 1- and 3-month rat study). The applicant acknowledged a potential treatment-related effect on female fertility with statements in section 5.3 of the SmPC based on ovarian findings reported in rats, i.e. decreased weight at ≥0.54-fold clinical exposure (≥0.3 mg/kg), and histopathological changes with oestrous cycle changes at 1.6-fold clinical exposure (1 mg/kg). In addition, decreased epididymal weight and testicular hypocellularity were seen in this group. These findings on male reproductive organs are reported in the SmPC and in the RMP.

In the dose-range finding embryo-foetal development studies, embryofoetal lethality was observed from the non-maternotoxic dose levels of 0.64 and 0.3 mg/kg/day in rats and rabbits, respectively. Various external malformations affecting the extremities (limbs, digits, and tail) were reported in one rat foetus in the group dosed at 3.0 mg/kg/day and considered as treatment-related taking into account the developmental toxicity profile of MEK inhibitors. Moreover, foetal body weight was also decreased in rats at ≥ 0.64 mg/kg/day. In both species, embryofoetal lethality was seen at subclinical exposure levels. This toxicological profile is consistent with the pharmacological activity of mirdametinib given the reported role of the MAPK pathway in the regulation of embryonic development. It is also consistent with that of other approved MEK inhibitors. Overall, mirdametinib is considered as a selective developmental toxicant, and the clinical relevance of drug-induced embryofoetal lethality identified in rats and rabbits cannot be excluded. This justifies strengthening the level of recommendation for use during pregnancy in the SmPC section 4.6. In addition, it is agreed with the applicant that definitive embryofoetal development and pre/postnatal development studies are not needed in view of this pharmacology-related developmental toxicity as mentioned in section 4.6 of the SmPC containing warnings related to the use of mirdametinib during pregnancy and breastfeeding. The absence of such studies is also reported in section 5.3 of the SmPC.

From both dose-range finding EFD studies conducted with mirdametinib and considering the data with other MEK inhibitors supporting a class effect, mirdametinib has toxic/lethal effects on embryo-foetal development. This justifies the absence of further DART studies and that the SmPC section 5.3 mentions that the EFD studies were exploratory studies and that definitive EFD studies and PPND studies were not conducted with mirdametinib. Women of childbearing potential should be advised that mirdametinib may cause foetal harm and to avoid becoming pregnant while receiving mirdametinib. It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment. A conservative approach is followed and the duration of contraception measures after the last dose is extended for male and female patients in line with the SWP/NcWP recommendations on the duration of contraception following the end of treatment with a genotoxic drug (EMA/CHMP/SWP/74077/2020 rev. 1*).Both male and female patients (of reproductive potential) should be advised to use effective contraception during and for 25 weeks after the last dose in women and 13 weeks in men. The effect of mirdametinib on the exposure of oral contraceptives has not been evaluated, therefore women using oral hormonal contraceptives should be recommended to add a barrier method (see sections 4.4, 4.5, 4.6 and 5.3 of the SmPC).

A marketing authorisation is currently sought for patients aged 2 years and older. No juvenile animal study (JAS) was conducted with mirdametinib. This is in line with the agreed PIP. In non-clinical studies, primary treatment-related toxicities were attributed to the pharmacological activity of mirdametinib in the GI tract, skin, cornea, liver, bone. Routine risk minimisation measures in the clinical setting, including the wording in the SmPC and package leaflet, are considered sufficient to

minimise these safety concerns, with the exception of physeal dysplasia. It is proposed to further evaluate this risk in a PASS (Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study).

The metabolite PD-0315209 was measured in repeat dose toxicity studies conducted with mirdametinib. The multiple of exposure is based on total AUC exposure. PD-0315209 could be considered characterised in rats and transgenic mouse studies. However, PD-0315209's exposures are too limited in dogs to be considered characterised. Clinical exposure could be considered sufficient. No dedicated genotoxicity studies with PD-0315209 were performed. Two quantitative structure-activity relationship (QSARs) studies were negative. In *in vivo* genotoxicity studies no PK analysis was performed but an assumption made from the repeated dose toxicity in rats indicated that PD-0315209 is between 1.6-10 at the high dose used in these studies. Therefore, it could be considered that studies with the parent are sufficient.

A 4-week investigative study was performed in rats to compare the toxicity of the R-enantiomer (mirdametinib) and S-enantiomer (PD-0326116); however, the methodology/design used in this study are too limited to compare toxic profiles between both enantiomers. The inter-conversion R- to S-enantiomer was demonstrated and measured in animals and in humans. The conclusion could be endorsed that the participation of the S-enantiomer in the overall target PD activity, if any, would be negligible. Animal interconversion is present but more limited (2%) than in humans. In addition, the clinical experience could be considered sufficient to waive additional animal studies.

Mirdametinib was equivocal in an *in vitro* mouse fibroblast phototoxicity assay at significantly higher concentrations than clinical exposures. A ^{14}C distribution rat study demonstrated that mirdametinib was not retained in the skin or eye. Therefore, the human risk could be considered as low, which is acceptable. Phototoxicity potential is reported in the non-clinical section of the RMP and in section 5.3 of the SmPC.

Overall, the toxicology package is considered adequate.

ERA

The log Pow/Dow was determined in a GLP study OECD107; the determined values at 3 different pHs were below 4.5, therefore, no further PBT assessment is considered needed. The PECsw was calculated with a refined Fpen based on the prevalence of the disease and the treatment regimen. The calculated PECsw with the refined Fpen is below the threshold value of 0.01µg/L, therefore phase 2 studies are not required.

Considering the above date, mirdametinib is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

The marketing authorisation is currently sought for patients aged 2 years and older. No juvenile animal study (JAS) was conducted with mirdametinib, in line with the adopted PIP. Routine risk minimisation in the clinical setting, including the measures specified in the SmPC and package leaflet, is sufficient to minimise the safety concerns for identified toxicities, with the exception of physeal dysplasia which will be characterised further via a PASS.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the application is considered approvable for the applied indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 6: Overview of clinical studies

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
A4581004	PK (food effect)	Phase 1, open label, single-dose, 2-stage study	Oral capsule 20 mg Single dose	Healthy Participants n=23	Single dose	Completed / Full
MEK-NF-101	PK, Metabolism, Mass Balance, and Safety	Phase 1, single centre, non-randomized, open-label study	[^{14}C] Mirdametinib Oral solute ion 4 mg Single dose	Healthy Participants N=8	Single dose	Completed / Full
MEK-NF-102	QT/QTc, Cardiac Safety	Phase 1, double blind, randomized, 4-treatment, 4-period crossover study	Mirdametinib oral solution 6 mg and 14 mg Single dose Blank solution (negative control) Single dose Moxifloxacin oral tablet (positive control) 400 mg Single dose	Healthy Participants N=57	1 dose of study treatment in each of the 4 treatments periods (on Days 1, 8, 15, and 22)	Completed / Full

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
A4581001	Safety, DLTs, MTD, RP2D, PK, and efficacy	Phase 1-2, multicentre, open-label, noncomparative study Phase 1: Dose escalation, PK, and PD Phase 2: 3-parallel arm, noncomparative, single-agent screening study in breast cancer, colorectal cancer, and melanoma	Oral solution Phase 1: 1 mg QD to 30 mg BID (int) 10 to 20 mg BID (cont.) Phase 2: 15 to 20 mg BID (int)	Participants with Advanced Cancer Phase 1: 66 Phase 2: 13	Phase 1: Continuous (without 1week holiday between cycles) Continuous with breaks (5 days on/2 days off) Phase 2: Intermittent (3 weeks on/1 week off)	Completed / Synopsis
A4581002	Safety, Tolerability	Phase 2, single arm, multicentre, open-label study	Oral capsule 15 mg BID (int)	Participants with Advanced Non-Small Cell Lung Cancer N=34	28-day cycle with 3 weeks on / 1 week off (Schedule 1) 28-day cycle with 5 days on / 2 days off for 3 weeks, followed by 1 week off (Schedule 2)	Terminated Early / Synopsis

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Healthy Participants or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
NF-106	Efficacy, Safety, Tolerability	Phase 2, open label, multicentre study	Oral capsule 2 mg/m^2 (int)	Adolescent and Adult Participants with NF1 PN 19 (2 Adolescents, 17 Adults)	4-week cycle (3 weeks on / 1 week off)	Completed/ Full
MEK-NF-201	Efficacy, Safety, Tolerability	Phase 2b, open label, multicentre, longitudinal study	Oral capsule Oral tablet 2 mg/m^2 (int)	Adult and Paediatric Participants with NF1-PN 114 (58 Adults 53 Paediatrics)	4-week cycle (3 weeks on / 1 week off)	Ongoing*/ Full

[14C]: Carbon-14 BID: Twice a day DLT: Dose-limiting toxicity Cont.: continuous Int: intermittent MTD: Maximum tolerated dose NF1: Neurofibromatosis type 1 PN: Plexiform neurofibroma QD: Once daily RP2D: Recommended Phase 2 dose *Primary analysis for treatment phase completed; long-term follow-up phase ongoing.

2.6.2. Clinical pharmacology

Two commercial formulations are proposed:

- A hard capsule supplied at two strengths 1 mg and 2 mg and,
- A tablet supplied at one strength 1 mg which can be swallowed whole or dispersed in water.

The clinical pharmacology programme for mirdametinib encompasses 6 completed clinical studies, 3 performed in healthy volunteers (see below), 2 in patients with advanced cancer (**A4581001** and **A4581002**) and one in the target population (**NF-106**), as well as one ongoing phase IIb study **MEK-NF-201** (pivotal study):

- One mass balance and metabolism study (**MEK-NF-101**)
- One biopharmaceutical study investigating the effect of food on mirdametinib PK (**A4581004**)
- A thorough QT/QTc study (**MEK-NF-102**).

A population PK analysis (PPK) was developed (Pop-pk-report) from which predicted exposure metrics were used as input for a TGI (Tumour growth inhibition) model and two exposure-response (ER) analysis (PKPD report). No physiologically based pharmacokinetic (PBPK) model was developed.

2.6.2.1. Pharmacokinetics

Methods

Bioanalysis

The developed methods for the quantification of mirdametinib (and its metabolite PD-0315209 or M15) in several matrix are considered adequate and comply with the acceptance criteria of the bioanalytical method validation of ICH guideline M10 on bioanalytical method validation and study sample analysis.

Pharmacokinetic analysis

For single or multiple-dose studies, PK parameters evaluated in plasma include Cmax, Clast, Cmin, Tmax, Tlast, AUCs (AUC0-t, AUC0-12, AUCtau, AUC0-∞), CL/F and Vz/F, AUC%extra, AI (accumulation index), λz, T1/2.

For the mass balance study, additional PK parameters as Aeu, Feu, Aef, Fef and CLR were calculated.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix WinNonlin v8.3 or later.

Absorption

Following a single dose as an oral solution of 4 mg mirdametinib containing approximately 80 µCi of ^{14}C-Mirdametinib in healthy volunteers (study MEK-NF-101), absorption was rapid with a Cmax approximately achieved at Tmax of 0.5h. Geometric mean Cmax was 158 ng/mL and AUCinf was 639 ng.h/mL.

Following a single dose of mirdametinib in adults, absorption was rapid with a Cmax achieved at a median Tmax of 1 h. At a 2 mg/m2 dose, in adults, geometric mean Cmax was 188.3 ng/mL and AUC0-8h 368.1 ng.h/mL. (study NF-106).

Following multiple doses of mirdametinib, absorption was rapid with a Cmax achieved at a median Tmax of 1 h. At a 2 mg/m2 dose, in adults geometric mean Cmax was 188 ng/mL and AUClast (0-4h) was 431 ng.h/mL. At the same dose, in paediatrics, geometric mean Cmax was 191 ng/mL and AUClast (0-4h) was 459 ng.h/mL (study MEK-NF-201).

Based on in vitro investigations, mirdametinib is a substrate of P-gp and BCRP.

Absolute bioavailability

The absolute bioavailability of mirdametinib has not been investigated.

BCS Classification

Based on in vitro investigations on solubility and in vivo investigations on permeability (MEK-NF-101), mirdametinib should be classified as a BCS class 3 compound (high solubility/low permeability).

Relative bioavailability/Bioequivalence

No relative bioavailability study was performed to bridge the PK between the capsule and the tablet formulations. However both formulations were investigated as part of the pivotal study MEK-NF-201, mainly in the paediatric population.

Following a dose of 2 mg/m^2 BID in paediatric participants, mirdametinib plasma Cmax and AUClast, as geometric mean (geometric CV%), were 217 ng/mL (47.0%) and 511 ng·h/mL (35.7%), respectively, in paediatric participants who received the tablet formulation, and 177 ng/mL (69.1%) and 430 ng·h/mL (50.2%), respectively, in paediatric participants who received the capsule formulation.

Distribution

Mirdametinib has a 99.7% protein binding mainly on albumin, a B/P of 0.61 and has a high distribution in tissue with a Vz/F estimated at 255 L.

M15 has a 99.75% protein binding.

Elimination

In the ADME study MEK-NEF-101 following a 4 mg dose of mirdametinib as an oral solution, mean T1/2 was 28h, CL/F was 6.34 L/h and CLR of 0.0347 L/h. Mirdametinib is highly metabolised. Unchanged mirdametinib accounted for 8% of the dose in faeces and 0.7% in urine.

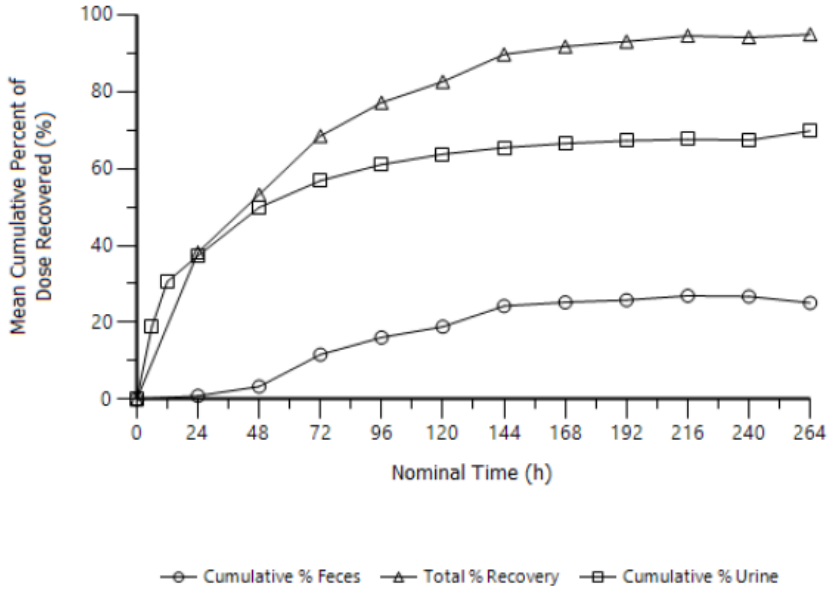
M15 has a mean T1/2 of 33.8h.

- Mass balance

The excretion and biotransformation of [14C]-mirdametinib was investigated in 8 healthy subjects following a single oral dose of 4 mg mirdametinib (solution) incorporating approximately 80 µCi [^{14}C]-mirdametinib.

The total recovery of radioactivity was 95% with approximately 67.7% and 27.3% of the dose recovered in urine and faeces respectively (Figure 2). Most of the administered radioactivity (90%) was recovered in the first 144 h post-dose.

Figure 2: Mean cumulative amount recovered in urine, faeces and total radioactivity (TRA) after administration of 80 µCI of 14C-mirdametinib



- Metabolism

Metabolite profiling was performed and approximately 16 metabolites were identified (Figure 3). In plasma, from AUC0-48h pooled samples, parent drug accounted for a mean of 35.3% of the total plasma radioactivity. M15, M22, and M30, accounted for 24.0%, 14.7%, and 6.4% of the radioactivity (mean across 8 subjects), respectively. M15 resulted from amide hydrolysis, M22 was a glucuronide conjugate of parent, and M30 was formed through oxidation/decarboxylation of glycerol side chain to aminooxyacetic acid. All other metabolites in the AUC0-48hr pooled samples represented less than 5% (mean across 8 subjects) of total circulating radioactivity.

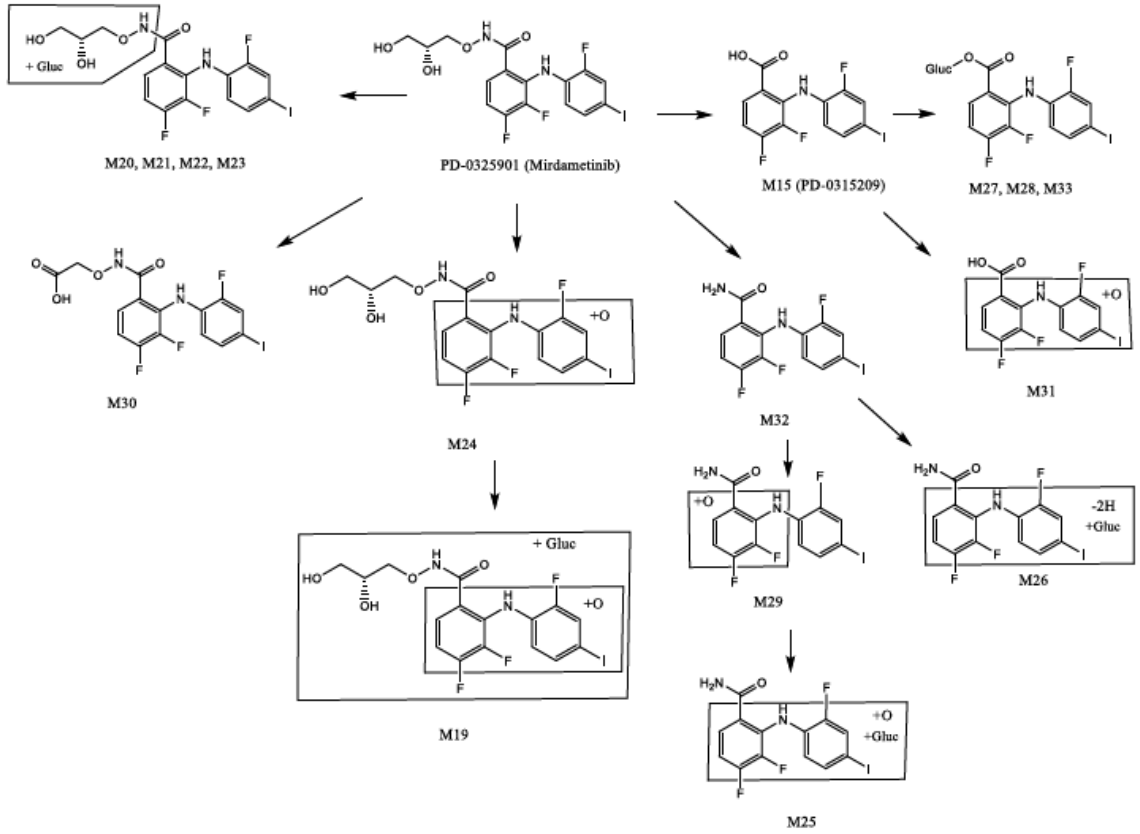
In urine, in addition to mirdametinib which accounted for a mean 0.7% of the dose, 12 metabolites were detected. The largest drug-related components were M21, M22, M33 and M20 which accounted for 19.8%, 14%, 11.9% and 7.7% of the dose, respectively. The remaining individual metabolites accounted for less than 3% of the dose. M20, M21 and M22 were identified as glucuronide metabolite from the parent. M33 is a glucuronide metabolite of M15. More than 94% of the dose excreted in urine was identified.

In faeces, in addition to mirdametinib which accounted for a mean 8.0% of the dose, 5 metabolites were detected. The largest drug-related components were M32 and M29 which account for 9.0 and 4.5% of the dose. More than 89% of the dose excreted in faeces was identified.

Overall mirdametinib was cleared mainly by metabolism with 8.7% of the dose recovered as unchanged. The primary metabolic clearance pathways involved were: 1) amide hydrolysis to the carboxylic acid with glucuronide conjugation (M33, 11.9% of the dose); 2) glucuronide conjugation (M20, M21, M22, and M23, 7.7%, 19.8%, 14.0%, and 3.1% of the dose, respectively); and 3) reductive hydrolysis (cleavage of the glycerol) to form the amide (M32, 9.0% of the dose). Other minor metabolites were observed with further metabolism (additional oxidation, glucuronide conjugation) through these pathways.

Based on in vitro investigation, CES1b was found to be the enzyme involved in the formation of M15. UGT1A6 and 2B7 were found to be involved in mirdametinib glucuronide conjugation.

Figure 3: Proposed metabolic scheme for mirdametinib in human subjects



Gluc = glucuronide. M27, M28, and M33 are acyl glucuronides

- Interconversion

Mirdametinib is chiral.

The inter-conversion from mirdametinib to its S enantiomer was investigated in studies A4581001 and A4581004. Following multiple doses of mirdametinib, the in vivo interconversion of mirdametinib to its S enantiomer was minor with mean R to S enantiomer ratios for AUCtau at Day 21 ranging from 0.01613 to 0.0389.

- Pharmacokinetic of metabolites

As part of the mass balance study MEK-NEF-101, based on AUC0-48h pooled samples in plasma, two major metabolites (>10%) were found PD-0315209 (M15; 24%) and M22 (14.7%). Across the clinical development the PK of M15 was investigated in all the studies.

M15 is an active metabolite with a less effective activity at reducing ERK phosphorylation in tumour cells growth in culture in the presence of 10% serum, exhibiting an IC50 of 1.3 µM compared with 0.59 nM for the parent compound (2200-fold higher IC50 for PD-0315209).

Dose proportionality and time dependencies

Mirdametinib dose proportionality is claimed between 1 to 30 mg. Steady-state is expected to be reached by approximately 6 days for mirdametinib (5 half-life) and 7 days for M15. The accumulation ratio for AUCtau for mirdametinib ranged from 1.1 to 1.9 and Z.4 to 3.9 for mirdametinib across a dose range from 1 to 30 mg.

Intra-and inter-individual variability

In the target population (study MEK-NF-201) after multiple doses, the inter individual variability (IIV) based on geometric CV% for mirdametinib PK was high for both Cmax and AUC0-4h.

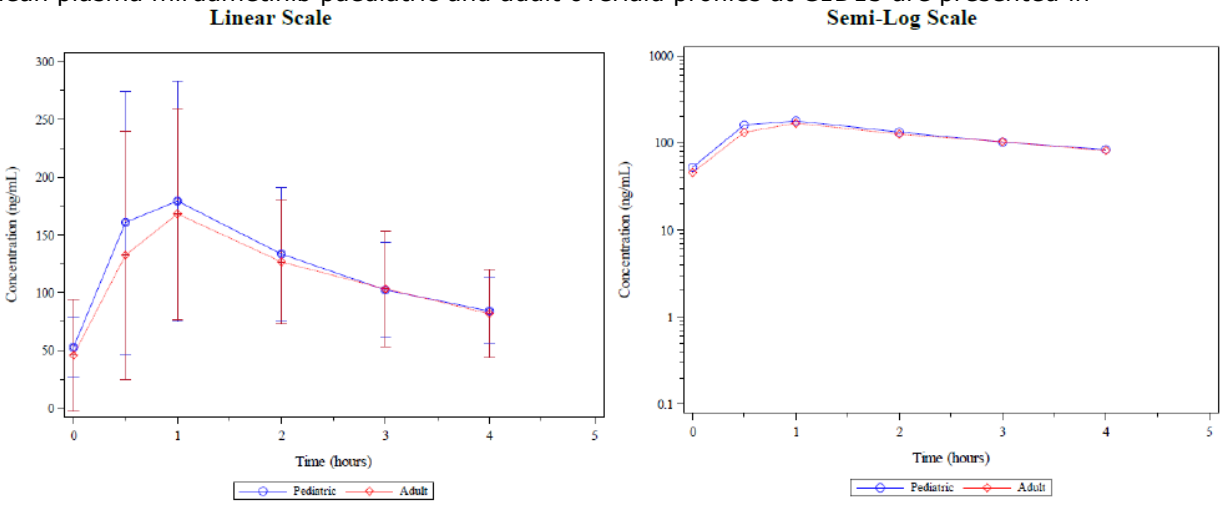
The intra-subject variability of mirdametinib based on CV% from a cross-over study (A4581004) was low for AUCinf (4.3%) to moderate for Cmax (20%).

Pharmacokinetics in the target population

Two clinical studies have investigated mirdametinib PK in NF1 patients with PNs (studies NF-106 and MEK-NF-201).

In study MEK-NF-201 (pivotal study), study treatment was administered orally at a dose of 2 mg/m2 twice daily (BID) with a maximum dose of 4 mg BID. Dosing was on a 28-day cycle (4-week course) with a 3-weeks on/1-week off schedule for up to 24 cycles. Mirdametinib was administered as capsule 1 or 2 mg or as tablet 0.5 or 1 mg following two dosing nomograms.

Mean plasma mirdametinib paediatric and adult overlaid profiles at C1D15 are presented in



and associated PK parameters in Table 7.

Figure 4: Mean plasma concentration of mirdametinib in paediatric and adult overlaid profiles at C1D15

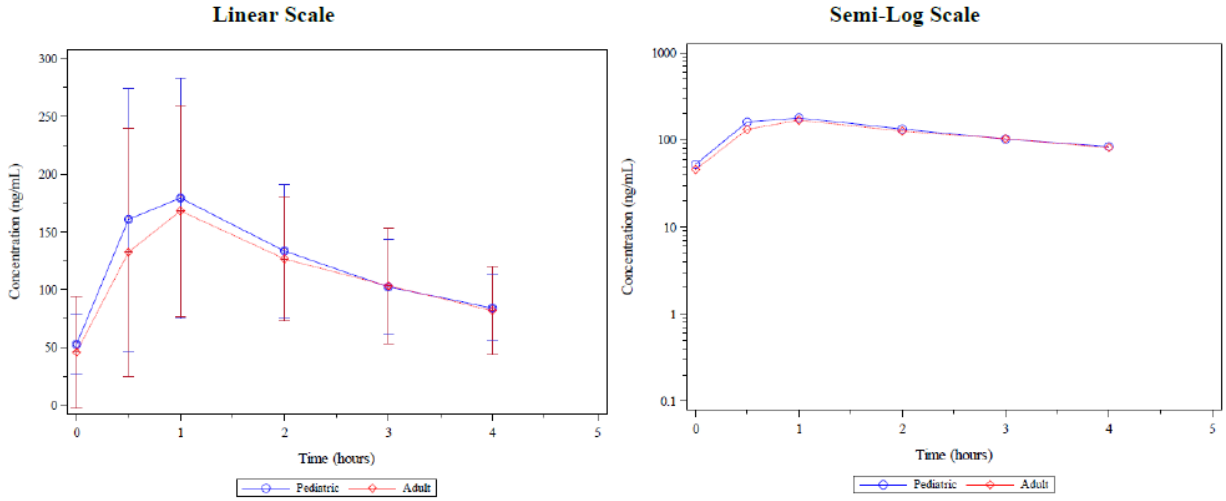


Table 7: Summary of plasma PK parameters for mirdametinib at C1D15

Parameter (Units)	Adult	Pediatric	Adult and Pediatric		Pediatric		Overall
Formulation	Both Formulations	Both Formulations	Tablet	Capsule	Tablet	Capsule	
Number of Participants	54*	53	21**	86	20	33	107
AUC_{last} (geometric CV%) (ng·h/mL)	431 (43.41)	459 (45.63)	507 (34.91)	431 (46.03)	511 (35.72)	430 (50.18)	445 (44.42)
C_{max} (geometric CV%) (ng/mL)	188 (51.98)	191 (61.72)	216 (45.67)	183 (58.78)	217 (46.97)	177 (69.07)	189 (56.61)
T_{max} (min-max) (h)	1.09 (0.00-4.17)	1.00 (0.00-4.00)	0.83 (0.42-3.02)	1.08 (0.00-4.17)	0.91 (0.42-3.02)	1.03 (0.00-4.00)	1.03 (0.00-4.17)
T_{last} (min-max) (h)	4.00 (3.83-4.25)	4.00 (3.83-4.18)	4.00 (3.90-4.13)	4.00 (3.83-4.25)	4.00 (3.90-4.13)	4.00 (3.83-4.18)	4.00 (3.83-4.25)

Abbreviations: AUClast: area under the concentration-time curve from time zero to the last quantifiable concentration Cmax: maximum observed plasma concentration CV% percent coefficient of variation; PK: Pharmacokinetic; Tlast: time of the last quantifiable concentration; Tmax: time to maximum observed plasma concentration.
*1adult participant received the tablet paediatric formulation (data were summarized with the adult capsule population)
**includes 1 adult participant who received the tabled formulation
Parameters are presented as geometric mean (geometric CV%) except for Tmax and Tlast presented as median (min-max)

Population Pharmacokinetic analysis (PPK)

Mirdametinib

One population pharmacokinetic analysis (PPK, Report pop-pk-report-1) aiming to characterize the PK of mirdametinib and M15 in healthy volunteers and in the target population, and to evaluate the effect of covariates on the variability of both compounds was developed. From this analysis predicted exposure metrics were used for the subsequent exposure-response (ER) analysis.

Methods

Five studies were included in the PPK analysis, one in healthy volunteers (study A4581004), two in patients with advanced malignancies (studies A4581001 and A4581002), and two in NF1 with PN patients (studies NF-106 and MEK-NF-201). The concentration-time data of mirdametinib and M15 were modelled using a compartmental approach. Covariates of interest in mirdametinib trials were baseline demographic covariates (age, body size, gender, race/ethnicity), formulation, dose, hepatic

function measure (albumin, bilirubin, alanine and aspartate amino transferase), renal function measure (CrCL), disease state and concomitant medications.

PPK was built using nonlinear mixed effects model with the importance sampling estimation (IMP) method for parameter estimation implemented in NONMEM (version 7.4, ICON Development Solutions, Elicott City, MD, USA). Covariates were tested manually without performing a Stepwise covariate model (SCM) approach. The PPK model was evaluated using standard diagnostic plots, visual predictive check. Instead of a bootstrap parameter uncertainty was evaluated using importance resampling (SIR).

Overall, the developed strategy aimed to characterize PK data from study MEK-NF-201 as the source of the most clinically relevant data. Other populations and studies were also optimized, where possible.

Results

A total of 4195 PK samples for mirdametinib from 260 subjects were available, PK data from the target population accounted for approximately half of the data/subjects (2086 observations/ 133 subjects).

The final PPK model consisted of a three compartment PK model with a transit compartment absorption model and linear elimination, in terms of number of transit compartment (NTR), mean transit time for fast or fed status (MTTs), CL/Fs, Vd/Fs (central, shallow and deep) and Frel. IIV was considered on all PK parameters except those from the shallow compartment (Q2/F and V2/F). Residual unexplained variability (RUV) was modelled using a proportional error.

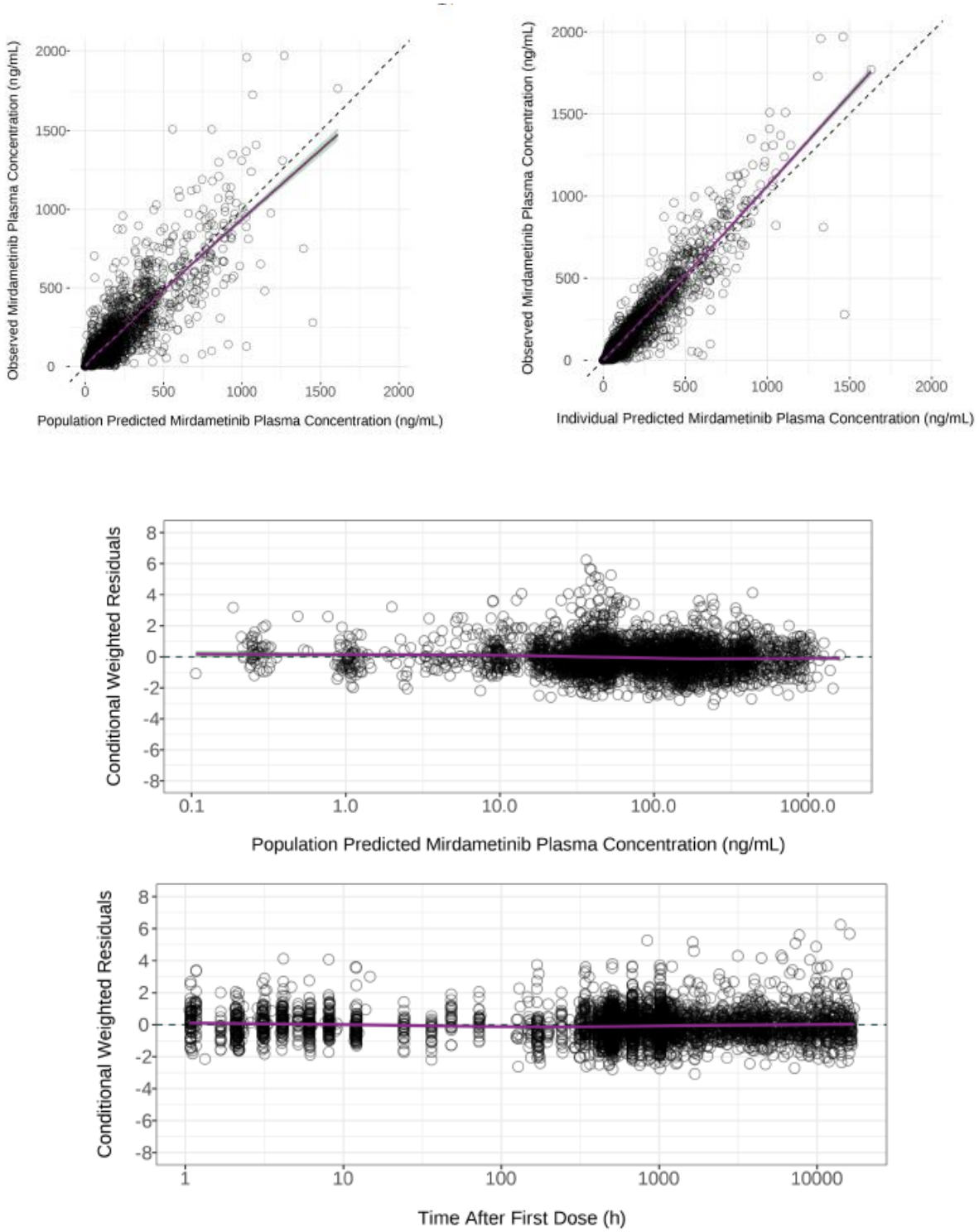
Eta-shrinkage was reasonable for CL/F (21.8%) and MTT (23.8%), moderate for V1/F (29%) and high for the other PK parameters ranging from 38.8% to 58.1% (Vc/F to Q2/F). The condition number was 214. BW allometric scaling on CL/F and Vc/F was considered with estimated coefficient of 0.631 and 0.586 respectively. A patient effect on Q2/F was estimated to be 8 L/h v 3.5 L/h in healthy participants, however confounding factor (healthy participant from one study and were Asian) can be an explanation.

Table 8: Parameter estimates of the final mirdametinib PPK model

Parameter	Descriptor	Estimate	CI95	CI95, SIR
θ_1	Apparent Clearance (L/h)	4.17	(3.88 - 4.49)	(4.06 - 4.38)
θ_2	Apparent Central Volume of Distribution (L)	16.0	(13.9 - 18.3)	(15 - 17.5)
θ_3	Apparent Intercompartmental Clearance - Shallow Compartment (L/h)	0.520	(0.469 - 0.577)	(0.479 - 0.561)
θ_4	Apparent Peripheral Volume of Distribution - Shallow Compartment (L)	22.4	(20.6 - 24.3)	(20.9 - 23.9)
θ_5	Apparent Intercompartmental Clearance - Deep Compartment (L/h)	8.16	(7.23 - 9.22)	(7.43 - 8.96)
θ_6	Apparent Peripheral Volume of Distribution - Deep Compartment (L)	54.3	(43.3 - 68.0)	(47.4 - 62)
θ_7	Number of Transit Compartments (n)	2.46	(1.84 - 3.30)	(1.86 - 3.14)
θ_8	Mean Transit Time - High-fat meal (h)	3.08	(2.30 - 4.13)	(2.56 - 3.53)
θ_9	Proportional Error	0.397	(0.368 - 0.426)	(0.382 - 0.413)
θ_{11}	Mean Transit Time - Fasted or Unknown food (ratio)	0.176	(0.0771 - 0.274)	(0.146 - 0.207)
θ_{12}	Relative Bioavailability - High-fat meal (ratio)	0.912	(0.872 - 0.953)	(0.882 - 0.946)
θ_{13}	Proportional Error - Study NF106	0.145	(0.108 - 0.181)	(0.12 - 0.18)
θ_{14}	Proportional Error - Study A4581004	0.208	(0.188 - 0.228)	(0.197 - 0.221)
θ_{16}	Apparent Intercompartmental Clearance Deep Compartment - Healthy Volunteers (ratio)	0.430	(0.354 - 0.506)	(0.356 - 0.488)
θ_{17}	Allometric Coefficient - Body Weight on Clearances	0.631	(0.429 - 0.832)	(0.569 - 0.719)
θ_{18}	Allometric Coefficient - Body Weight on Volumes of Distribution	0.586	(0.0938 - 1.08)	(0.41 - 0.671)
$\omega_{1.1}$	$\omega^2_{ApparentClearance}$	0.0714	(0.0500 - 0.0928)	(0.0523 - 0.0909)
$\omega_{2.2}$	$\omega^2_{ApparentCentralVolumeofDistribution}$	0.172	(0.0753 - 0.268)	(0.103 - 0.271)
$\omega_{5.5}$	$\omega^2_{ApparentIntercompartmentalClearance-DeepCompartment}$	0.0476	(0.0102 - 0.0850)	(0.0144 - 0.0812)
$\omega_{6.6}$	$\omega^2_{ApparentPeripheralVolumeofDistribution-DeepCompartment}$	0.647	(0.0809 - 1.21)	(0.426 - 0.922)
$\omega_{7.7}$	$\omega^2_{NumberofTransitCompartments}$	0.779	(0.327 - 1.23)	(0.357 - 1.2)
$\omega_{8.8}$	$\omega^2_{MeanTransitTime}$	0.574	(0.331 - 0.817)	(0.396 - 0.737)
$\omega_{9.9}$	$\omega^2_{RelativeBioavailability}$	0.0235	(0.00363 - 0.0434)	(0.0085 - 0.0389)

CI95: 95% Confidence interval; ω^2_X: variance of inter-individual variability of parameter X. **SIR:** Sampling Importance Resampling

Figure 5. GOF plots for the final PPK model



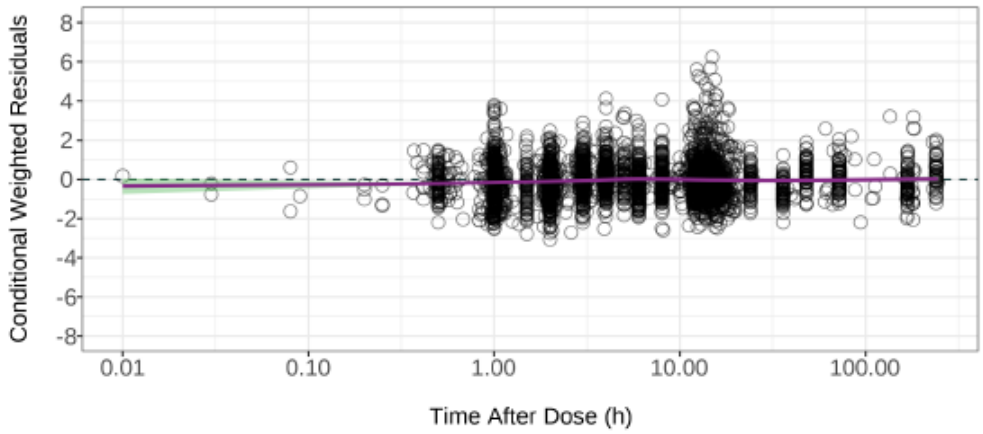
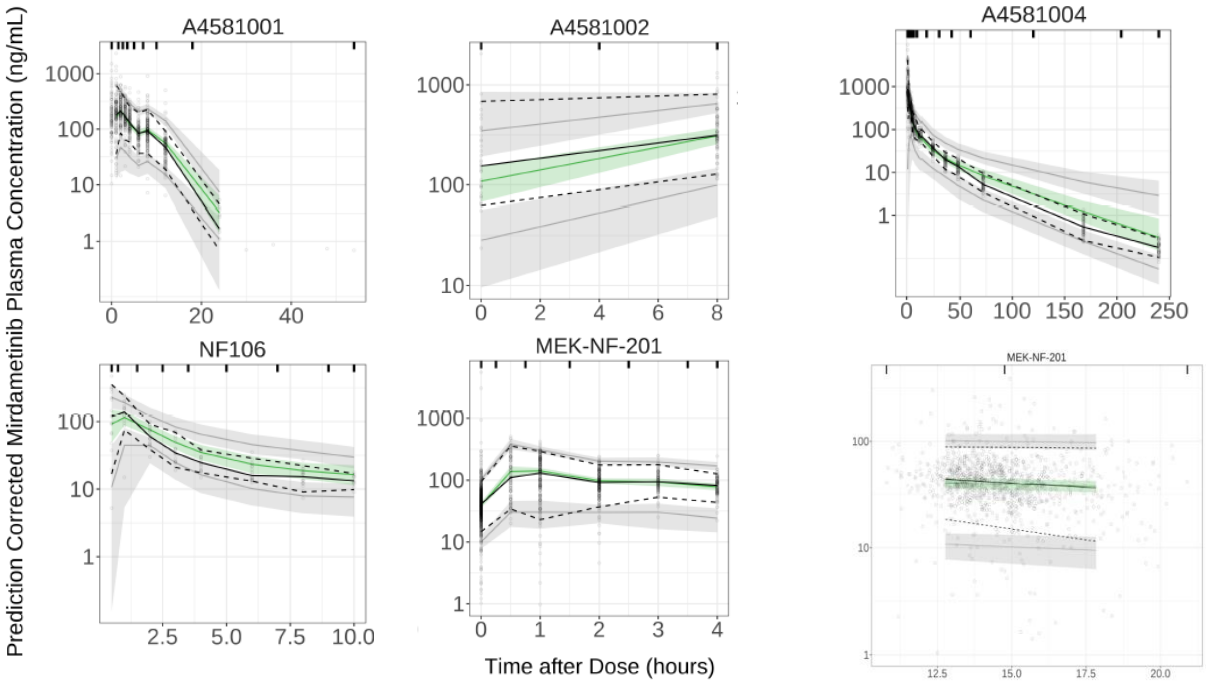


Figure 6: pcVPC by study for mirdametinib



PD-0315209 (M15)

Methods

The metabolite model was developed sequentially, starting with the mirdametinib model. Empiric Bayes estimates (EBEs) from the mirdametinib PopPK model were used to predict mirdametinib concentrations, and M15 PK was driven by Fm and the mirdametinib elimination rate constant. Fm was fixed at 0.184.

Results

A total of 4218 PK samples for M15 from 260 subjects were available. The final PPK model consisted of a three compartment PK model. Parameterized by CLm/Fs, Vdm/Fs (central, shallow and deep). An

omega block was used and IIV was considered on all PK parameters except those from the shallow compartment (Q2m/F and V2m/F). RUV was modelled using a combined error model.

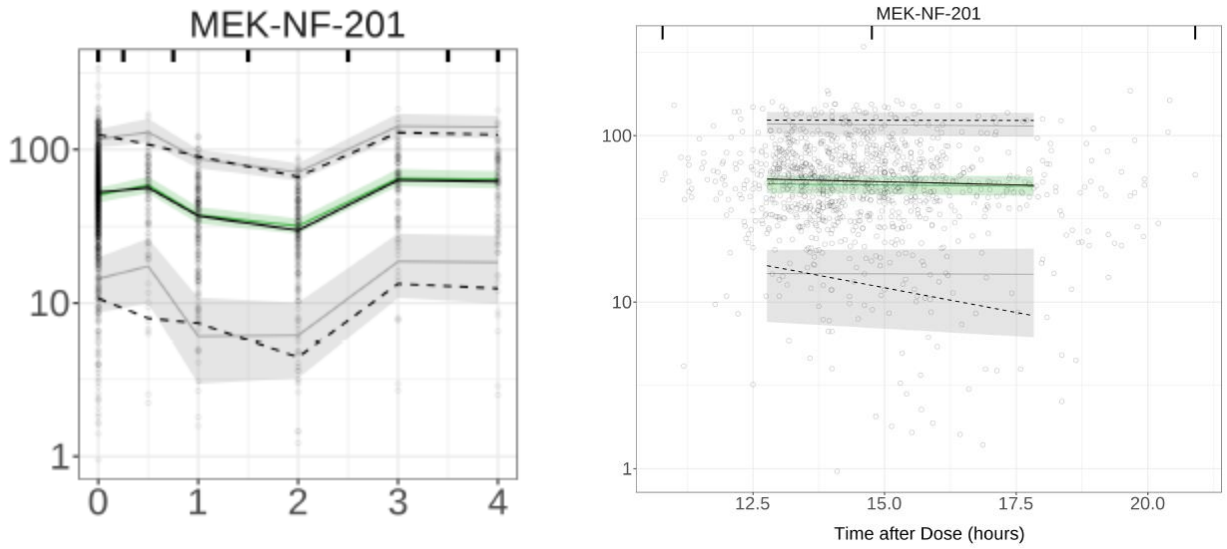
Overall PK parameters were estimated with good precision (as suggested by the results from the MCMC) except the additive error, some of the diagonal elements of the omega block and Vms/F and the IIV of CLm/F which were outside the 95%CI from the posterior distribution. Eta-shrinkage was low for CLm/F (21.6%) and Fm (18.1%), moderate for the other parameters ranging from 28.2% to 34.2% (Vm1/F to Qm1/F). The condition number was 2002 suggesting instability. Allometric scaling with time varying weight on CL/F and Vc/F was considered with fixed and estimated coefficient of 0.75 and 0.652 respectively. An effect of age and UGT2B7 inducer on Fm and an effect of CLCr on Clm were found.

Table 9: Parameter estimates of the Final M15 PPK model

Parameter	Descriptor	Estimate	CI95	CI95, MCMC
θ_1	CLm/F, Apparent Clearance PD-0315209 (L/h)	0.583	(0.536 - 0.635)	(0.522 - 0.614)
θ_2	Apparent Central Volume of Distribution (L)	0.700	(0.231 - 2.12)	(0.149 - 0.653)
θ_4	Apparent Intercompartmental Clearance - Deep Compartment (L/h)	4.77	(3.01 - 7.54)	(3.9 - 7.27)
θ_5	Apparent Peripheral Volume of Distribution - Deep Compartment (L)	3.90	(3.51 - 4.34)	(3.4 - 4.65)
θ_6	Apparent Intercompartmental Clearance - Shallow Compartment (L/h)	0.446	(0.382 - 0.520)	(0.314 - 0.49)
θ_7	Apparent Peripheral Volume of Distribution - Shallow Compartment (L)	5.48	(4.65 - 6.46)	(1.48 - 1.79)
θ_8	Proportional Error	0.273	(0.244 - 0.302)	(0.271 - 0.285)
θ_9	Additive Error	0.0742	(0.00550 - 0.143)	(-0.0639 - 0.0656)
θ_{10}	Allometric Coefficient - Time-Varying Weight on Clearances	0.750	NC	(0.75 - 0.75)
θ_{11}	Allometric Coefficient - Time-Varying Weight on Volumes of Distribution	0.652	(0.652 - 0.652)	(0.525 - 0.974)
θ_{12}	Creatinine Clearance on CLm/F (power)	0.225	(0.225 - 0.225)	(0.0102 - 0.372)
θ_{14}	UGT2B7 Inducer on logit of Fm (ratio)	0.854	(0.635 - 1.07)	(0.792 - 1.02)
θ_{15}	Age on Fm (power)	-0.148	(-0.148 - -0.148)	(-0.204 - -0.105)
$\omega_{1.1}$	$\omega^2_{ApparentClearanceoftheMetabolite}$	0.351	(0.155 - 0.547)	(0.385 - 0.84)
$\omega_{2.1}$	$\omega^2_{CovarianceCLm-V5}$	-0.198	(-0.643 - 0.247)	(0.0944 - 1.97)
$\omega_{2.2}$	$\omega^2_{ApparentCentralVolumeofDistributionoftheMetabolite}$	2.65	(-0.0313 - 5.32)	(3.8 - 10.2)
$\omega_{3.1}$	$\omega^2_{CovarianceCLm-Fm}$	-0.237	(-0.394 - -0.0789)	(-0.518 - -0.237)
$\omega_{3.2}$	$\omega^2_{CovarianceV5-Fm}$	0.151	(-0.207 - 0.509)	(-1.3 - 0.0459)
$\omega_{3.3}$	ω^2_{Fm}	0.247	(0.133 - 0.361)	(0.225 - 0.408)
$\omega_{4.1}$	$\omega^2_{CovarianceCLm-Q56}$	0.306	(0.0535 - 0.559)	(0.167 - 0.634)
$\omega_{4.2}$	$\omega^2_{CovarianceV5-Q56}$	-0.452	(-1.01 - 0.102)	(-0.994 - 1.19)
$\omega_{4.3}$	$\omega^2_{CovarianceFm-Q56}$	-0.213	(-0.391 - -0.0355)	(-0.443 - -0.103)
$\omega_{4.4}$	$\omega^2_{ApparentIntercompartmentalClearance-Deep}$	0.432	(0.126 - 0.738)	(0.264 - 1)
$\omega_{5.1}$	$\omega^2_{CovarianceCLm-V6}$	0.264	(0.0104 - 0.518)	(0.261 - 0.709)
$\omega_{5.2}$	$\omega^2_{CovarianceV5-V6}$	-0.409	(-1.15 - 0.336)	(-0.502 - 1.46)
$\omega_{5.3}$	$\omega^2_{CovarianceFm-V6}$	-0.178	(-0.403 - 0.0475)	(-0.477 - -0.18)
$\omega_{5.4}$	$\omega^2_{CovarianceQ56-V6}$	0.313	(0.104 - 0.521)	(0.198 - 0.771)
$\omega_{5.5}$	$\omega^2_{ApparentPeripheralVolumeofDistribution-Deep}$	0.269	(0.0673 - 0.470)	(0.259 - 0.818)

CI95: 95% Confidence interval; ω^2_X: variance of inter-individual variability of parameter X. **MCMC:** Markov Chain-Monte Carlo

Figure 7: pcVPC plot for study MEK-NF-201 for M15



Special populations

Renal impairment

No formal PK study investigating the effect of renal impairment on mirdametinib and M15 PK was performed. The effect of CLCr on mirdametinib and M15 PK was investigated as part of the PPK analysis.

Hepatic impairment

No formal PK study investigating the effect of hepatic impairment on mirdametinib and M15 PK was performed. m

Ethnicity

No formal PK study investigating the effect of race on mirdametinib and M15 PK was performed.

Age

No formal investigations with regard to age has been performed.

Weight

Based on the PPK analysis CL/F and Vc/F for both compounds increased allometrically with weight.

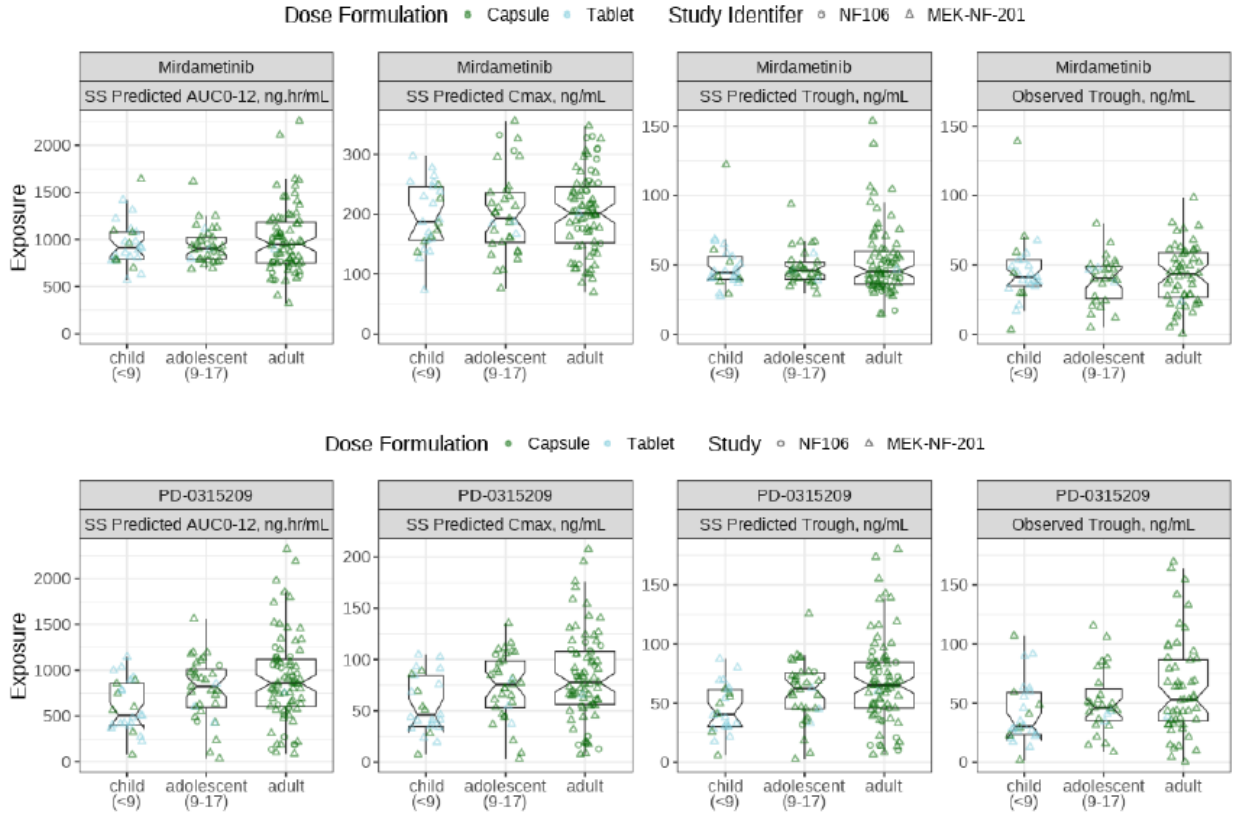
Gender

No formal investigations with regard to gender has been performed.

Paediatric population

From the target population (study NF-106 and MEK-NF-201) a total of 58 subjects aged 2 to 17 years were enrolled and received mirdametinib dose of 2 mg/m^2 BID (max 4 mg).

Figure 8: Predicted and observed steady-state exposures by subpopulation



	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	21/113	13/113	1/113

Exposure-response

In the current submission, the PK/PD model and the two ER analysis are considered supportive to the dose selection. Overall the main drivers of both efficacy (TGI PK/PD and Best overall response - BOR) and safety endpoints was the AUC0-12,ss of mirdametinib.

Dose rationale

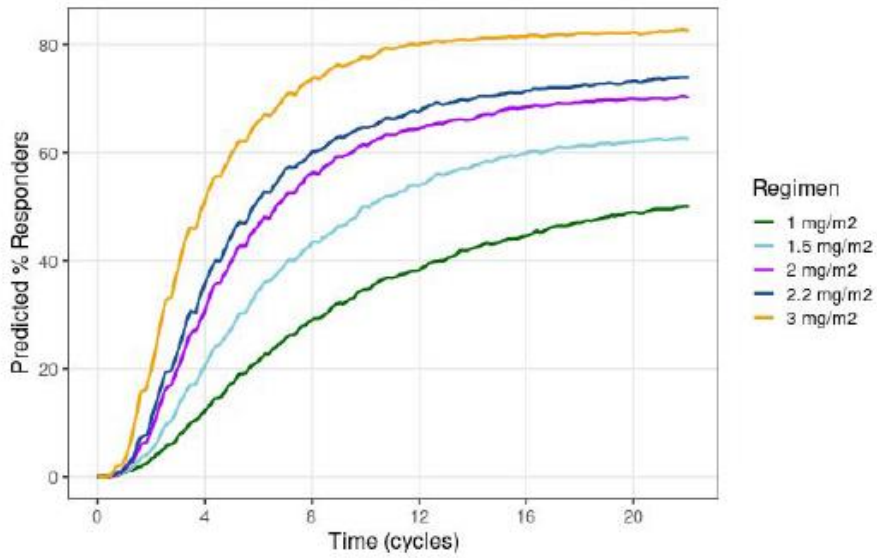
Based on study A4581001, it was shown that doses ≥ 2 mg BID were associated to a ≥ 60% suppression of the pERK activity.

Based on nonclinical data, the range of IC50s for inhibition of pERK was between 5.17 ng/mL (MiaPaCa-2) and 53.5 ng/mL (HT-29. The predicted Cavg,ss in human participants with NF1 PN at steady state of the proposed clinical dose is 77.6 ng/mL.

Based on the supportive data from study NF-106, a mirdametinib dose of 2 mg/m^2 (maximum 4 mg BID) on a 3 weeks on/1 week off schedule was selected for the pivotal Study MEK-NF-201. Simulations were performed to estimate the TGI response through 24 cycles (Figure 9) and the incidence of safety endpoints in which significant ER relationship were identified (

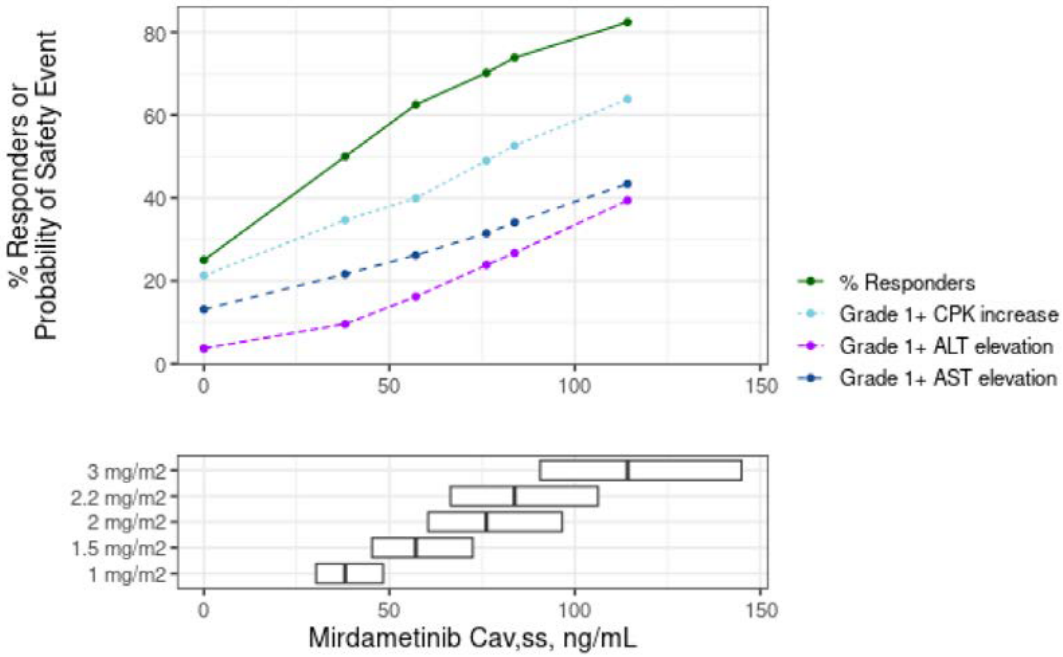
).

Figure 9: Population simulation of response rate over time at various mirdametinib dose levels



An improvement in efficacy was predicted up to the 2.0 mg/m2 BID dose regimen, with response rate increasing from 50.3% at 1.0 mg/m2 to 71.3% at 2.0 mg/m2. Conversely, smaller increases in probability of safety events were predicted with increasing dose, with the predicted incidence from the 1.0 to 2.0 mg/m2 dose level increasing from 9.6% to 23.9% for Grade ≥1 ALT elevation, 21.6% to 31.5% for Grade ≥1 AST elevation, and 34.7% to 49.0% for Grade ≥1 CPK increase.

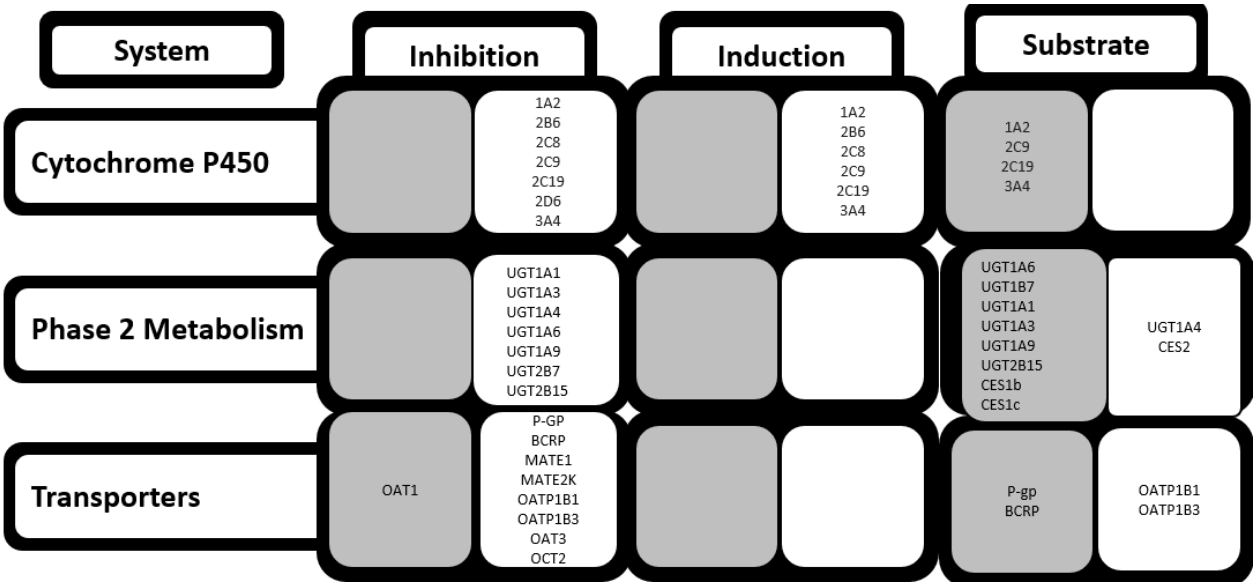
Figure 10: Response rate and probability of safety events at various mirdametinib dose levels as a function of mirdametinib Cavg,ss



Pharmacokinetic interaction studies

Figure 11 and Figure 12 display the results from in vitro studies on the investigations of drug interactions performed by the applicant with mirdametinib and its active metabolite PD-0315209:

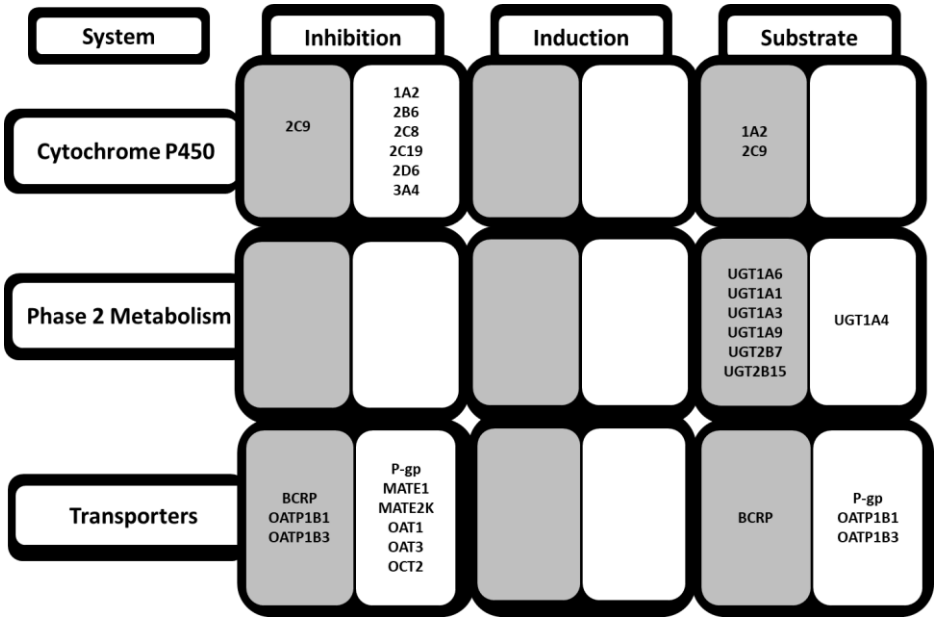
Figure 11: In vitro drug interaction evaluations for mirdametinib



Abbreviations: BCRP: breast cancer resistance protein; CES: carboxyl esterase; MATE: multidrug and toxin extrusion protein; OAT: organic anion transporter; OATP: organic anion transporting polypeptide; OCT: organic cation transporter; P-gp: P-glycoprotein; UGT: uridine diphosphate glucuronosyltransferase.

Figure represents in vitro findings that were not evaluated in clinical studies. The grey boxes describe positive findings, and the white boxes describe negative findings.

Figure 12: In vitro drug interaction evaluations for PD-0315209



Abbreviations: BCRP: breast cancer resistance protein; MATE: multidrug and toxin extrusion protein; OAT: organic anion transporter; OATP: organic anion transporting polypeptide; OCT: organic cation transporter; P-gp: P-glycoprotein; UGT: uridine diphosphate glucuronosyltransferase.

Figure represents in vitro findings that were not evaluated in clinical studies. The grey boxes describe positive findings, and the white boxes describe negative findings.

▪ *In silico*

No PBPK modelling and simulations have been performed.

▪ *In vivo studies*

No clinical dedicated drug-drug interactions studies have been performed.

Potential interaction with oral contraceptives

Studies to assess the DDI potential with combined oral contraceptives have not been conducted at this time.

Potential interaction with acid-reducing agents

Mirdametinib does not demonstrate pH-dependent solubility. The maximum clinical dose of mirdametinib is 4 mg BID, which is expected to require a solubility of 0.016 mg/mL (4 mg/250 mL).

2.6.2.2. Pharmacodynamics

Mechanism of action

Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). Mirdametinib blocks MEK activity and the rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-MEK pathway. Therefore, MEK inhibition blocks proliferation and survival of tumour cells in which the RAF-MEK-extracellular related kinase (ERK) pathway is activated.

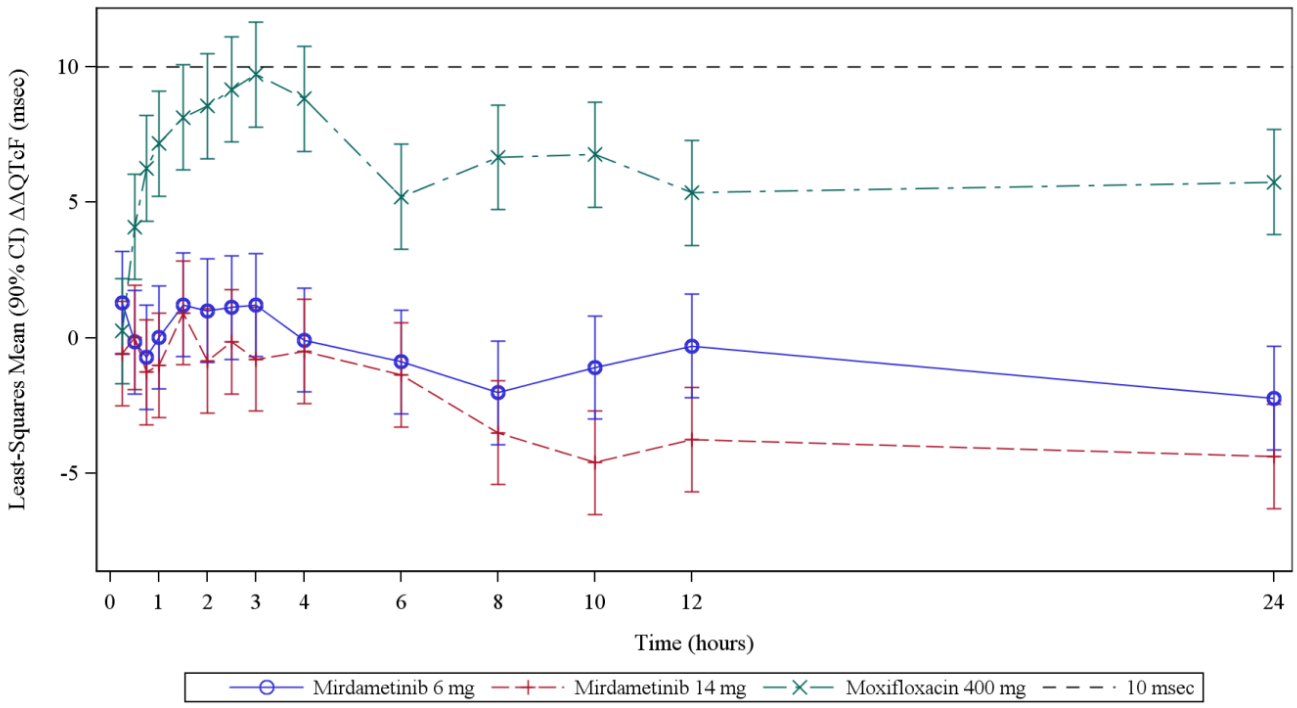
Primary and Secondary pharmacology

Mirdametinib inhibits MEK with a Ki for the activated forms of MEK1 and MEK2 at ≤ 1.1 nM. In a select panel of 104 kinases, 100 were completely refractory to inhibition after treatment with 1 μM mirdametinib.

▪ A thorough QT/QTc study was performed during study MEK-NF-102, a phase 1, double-blind, randomized, 4-treatment, 4-period crossover study in healthy adult patients to evaluate the effects of mirdametinib and its primary metabolite (PD-0315209) on cardiac repolarization, as detected primarily by QT/QTc prolongation. Patients were randomized to treatment sequence and received the following treatments separated by 7-day washout periods: open-label moxifloxacin tablet, placebo oral solution, 6 mg mirdametinib oral solution, and 14 mg mirdametinib oral solution. Single doses of 6 and 14 mg mirdametinib were selected for this study to approximate steady-state therapeutic and supratherapeutic exposures, respectively.

Moxifloxacin 400 mg was used as a positive control (open-label) to establish assay sensitivity. The applicant has therefore complied with the ICH E14 note for guidance and provided a phase 1 study (MEK-NF-102) which primary objective was to evaluate the relationship between plasma concentrations after oral administration of single doses of mirdametinib (6 mg or 14 mg) and time-matched, placebo-corrected, baseline-adjusted difference in the corrected QT interval of electrocardiogram (ECG) (QTc) using Fridericia's formula (QTcF) (ΔΔQTcF). For ICH E14, the threshold level of regulatory concern is around 5ms, as evidenced by an upper bound of 10 ms of the 95% confidence interval around the mean effect.

Figure 13: ΔΔQTcF versus time showing least-squares mean differences and 2-sided 90 % confidence bounds (safety analysis set)



Abbreviations: ΔΔQTcF, time-matched, placebo-corrected, baseline-adjusted difference in QTcF; QTcF, corrected QT interval of electrocardiogram using Fridericia's formula.
The placebo and mirdametinib 6 and 14 mg treatments were administered orally as a 140 mL solution; moxifloxacin 400 mg treatment was administered orally as a tablet. One subject's values collected at the 0.75 h time point for placebo treatment were excluded from this analysis due to the extraction of the data after the 1 h time point.

2.6.3. Discussion on clinical pharmacology

Clinical pharmacokinetics

Bioanalytical method

Three different methods (Report 764-04368/04369, 05479VDAC PLC with addendum, 230372VCWB) to quantify mirdametinib, its main metabolite (M15) with or without the S-mirdametinib in human plasma or urine, were developed from 2003 to 2023 (data not shown). No evidence of a cross-validation analysis between these three methods has been performed given the timelines between the end of study A4581004 and study NF-106. From the PPK analysis, bioanalytical methods were not investigated as a covariate, however a different RUV model was used for studies NF-106 and A4581004.

BCS classification

Based on in vitro investigations on solubility and permeability, the applicant classified mirdametinib as a BCS 1 compound. Based on the ICH M9 guideline, permeability should preferentially be based on the extent of absorption derived from human PK studies e.g. absolute bioavailability or mass balance. Permeability can be also assessed by validated and standardized in vitro methods using Caco-2 cells.

Absolute bioavailability has not been determined.

Results from the mass balance study MEK-NEF-101 indicated that approximately 67.7±4.59% of the mirdametinib dose was excreted in urine (0.7% unchanged) and 27.3±4.38% in faeces (8% unchanged) suggesting that at least 67.7% of the dose reach the systemic circulation. Excreted

material in faeces were the unchanged mirdametinib (8%), M15 (1.9%), M23/M24 (0.2%), M29 (4.5%), M31 (1.2%) and M32 (9%). M23/M24, M15, M29, M31 are either glucuronide or oxidative metabolites then the fraction absorbed could be estimated at 71%. Therefore since no in vivo data can demonstrated a fa ≥85%, mirdametinib should be classified as a BCS 3 compound.

Relative bioavailability/ Bioequivalence

No formal BE study was performed between the two formulations (capsule and tablet). Both formulations have been administered as part of the pivotal study, and compared to the commercial formulation, it is not expected that the minor changes (sweetener and grape flavour) will affect their in vivo performance.

Based on the PK data from study MEK-NF-201, after multiple doses of mirdametinib and based on sparse PK sampling, it seems that the PK exposure observed with the tablet formulation is slightly higher than those of the capsule (217 vs 177 ng/mL for Cmax and 511 vs 430 for AUClast) in children. However no strong conclusion could be drawn from these results.

Distribution / Elimination:

Following a single oral dose of 4 mg [14C]mirdametinib in healthy subjects, the mean apparent volume of distribution of mirdametinib was 255 L. Human plasma protein binding is >99%. Mirdametinib is mainly bound to human serum albumin (>99%). In healthy adult subjects, following a single dose of 4 mg of radiolabelled mirdametinib, 68% of the dose was recovered in urine (0.7% unchanged) while 27% was recovered in faeces (8.7% unchanged in urine and faeces). The mean terminal half-life is 28 hours. The apparent systemic clearance (CL/F) is 6.34 L/h (see section 5.2 of the SmPC).

Metabolite profiling

Radio profiling of the AUC48h plasma revealed the presence of a unique metabolite M30 in plasma that was not detected in non-clinical investigations. Based on individual data except one subject, M30 range from 3.5 to 9.7% of plasma TRA (mean 6.4±2.8%), therefore it cannot be ruled out with a pooled AUC48-t_{last} that M30 will be considered also as a major metabolite (>10%). The CHMP did not agree with the applicant's justification that >95% of the circulating radioactivity was represented in the AUC0-48h pool whereas time points 48 to 168 hours only represented ~3% of the radioactivity. Since the estimated half-life of plasma TRA was 39.1 h, the AUC0-48h covers largely less than 2 plasma TRA half-life (1.2). After calculation based on the raw data, the AUC0-48h pool represents 70% (min-max: 65-75%) of the circulating radioactivity therefore suggesting that the AUC0-48h pool is truncated. The applicant is therefore recommended to:

- Investigate if M30 is an active metabolite, given its similar structure to the parent compound, CH2OH-CHOH moiety replaced by a COOH, **Error! Reference source not found.**, (REC). For this aspect, the applicant commits to provide the result of this investigation (REC) which was deemed acceptable, considering the need to performing M30 chemical synthesis and developing a dedicated bioanalytical method for its PK characterization (see below).
- Characterize the PK of M30 in the target population. For this aspect, the applicant commits to provide this characterization as part of two planned clinical DDI studies (REC) since no available PK samples from the pivotal study MEK-NF-201 were available for a retrospective analysis.

In the eventuality that the metabolite M30 is found to be a major metabolite after the aforementioned PK characterisation, the MAH committed to perform an appropriate nonclinical qualification in accordance with ICH M3(R2).

Genetic polymorphism

CES1b, UGT1A6 and UGT2B7 genetic polymorphism on mirdametinib metabolism is considered minor.

Population Pharmacokinetic (PPK)

Overall all PK parameters were estimated with a good precision (as suggested by the results from the SIR). Eta-shrinkage was reasonable for CL/F (21.8%) and MTT (23.8%), moderate for V1/F (29%) and high for the other PK parameters ranging from 38.8% to 58.1% (Vc/F to Q2/F). The condition number was 214. BW allometric scaling on CL/F and Vc/F was considered with estimated coefficient of 0.631 and 0.586, respectively.

The metabolite model was developed sequentially, starting with the mirdametinib model for PD-0315209 (M15), the overall PK parameters were estimated with a good precision. An effect of age and UGT2B7 inducer on Fm and an effect of CLCr on Clm were found.

The developed PPK models for mirdametinib and M15 had a medium impact. Overall, their main objective to describe the PK in NF1 patients with PNs is fulfilled, however for the other populations the same conclusion cannot be claimed. and, for future development it is highly recommended to focus on the more recent PK data. To note, the three compartment PK model with Transit compartment absorption model (TCAM) absorption and first-order elimination will probably adequately fit the PK data from A4581004 (food effect study). However, in the target population the food status is unknown, thus there is no need for the TCAM, and these PK data will support a 2 compartment PK model. With a BID administration, there is no need for a three compartment. In addition, run times will be less prolonged allowing to perform a SCM for covariate search.

The PPK models were also used by simulation to propose a combined nomogram (Table 1) for both the dispersible tablet and capsule formulations whereas in the pivotal study MEK-NF-201 two separate nomograms (for each formulation) were applied. However, since correlation was observed between BW, age and formulation, the true effect of formulation (which is age dependent) and BW on mirdametinib PK cannot be distinguishable. Any formulation effect would have been identifiable if a formal BE study has been performed between the two available formulations which is not the case.

Despite these limitations, the observed exposure in subjects receiving capsules using the capsule nomogram and in subjects receiving tablets using the tablet nomogram is similar.

Overall, the use of a common nomogram would provide optimal and simplified dosing instructions for the calculation of the BSA-related dosing and dose adjustments and it would reduce the possible dosing errors between capsule and tablet switches.

Renal impairment

In the target population, 73.1% had a normal renal function, 23.1% had a mild and 3.85% a moderate impaired renal function. CLCr was not found to have a significant effect on mirdametinib PK. No dose adjustment is recommended in patients with mild or moderate renal impairment based on a population pharmacokinetic analysis. Ezmekly has not been studied in patients with severe renal impairment (CrCL ≥ 15 to < 30 mL/min) or patients with end stage renal disease (ESRD), and therefore, no dose recommendations can be made.

Hepatic impairment

As part of the PPK analysis, liver function biomarker (albumin, bilirubin, AST, ALT) were investigated as a covariate and were not found to have a significant effect on mirdametinib PK.

However, mirdametinib is extensively metabolized, and the extent of the liver involvement is unknown, and it is not a narrow therapeutic index drug. Consequently, use in patients with moderate or severe hepatic impairment should be considered to have potential effects on the PK of mirdametinib, and therefore no dose recommendation in this population can be made.

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin > ULN to 1.5x ULN or total bilirubin ≤ ULN and AST > ULN), based on a population pharmacokinetic analysis. Ezmekly has not been studied in patients with moderate or severe hepatic impairment, and therefore, no dose recommendation can be made

The applicant has planned to conduct a hepatic impairment study to assess the effects of hepatic impairment on the PK of mirdametinib. The study will evaluate varying degrees of liver dysfunction based on multiple evaluation criteria (REC).

Ethnicity

In the target population White, Black or African American, Asian, Others and American Indian accounted for 70.6%, 15.8%, 4.5%, 8.3% and 0.7%, respectively.

As part of the PPK analysis, race was investigated as a covariate and was not found to have a significant effect on mirdametinib PK.

Age

The effect of age on mirdametinib PK was investigated as part of the PPK analysis.

In the target population age ranged from 2 to 69 years. No relation was found with mirdametinib PK.

Weight

Based on the PPK analysis CL/F and Vc/F for both compounds increased allometrically with weight.

Gender

No formal investigations with regard to gender has been performed. The effect of gender on mirdametinib PK was investigated as part of the PPK analysis. No relation was found.

Breast-feeding women

There are no data regarding the presence of mirdametinib or its metabolites in either human or animal milk, its effects on a breastfed child, or on milk production. There were no reports of exposure to mirdametinib via lactation. A risk to the breast-fed child cannot be excluded, therefore breast-feeding should be discontinued during treatment with Ezmekly and should not be resumed for 1 week after the last dose (see section 4.6 of the SmPC).

▪ Pharmacokinetic drug-drug interactions (PK DDI)

In vitro

In vitro studies showed that mirdametinib is mostly metabolized by UGT enzymes, mainly UGT1A6 and 2B7, and also undergoes hydrolysis by CES1 which leads to the main active metabolite PD-0315209. No in vivo studies assessing the impact of an inducer or an inhibitor of these enzymes have been performed. The impact of UGT inducers, inhibitors and CES1 inhibitors on mirdametinib clearance through the PopPK analysis was tested and no association of exposure changes for mirdametinib and PD-0315209 with concomitant use of UGT1A6 inhibitors or inducers or CES1 inhibitors were identified.

In addition, a PBPK modelling and simulations was performed to predict the magnitude of the effect of probenecid, as an UGT2B7 inhibitor, and of rifampicin, as an UGT2B7 inducer. However, the PBPK platform was considered not sufficiently qualified according to the Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (EMA/CHMP/458101/2016, 13 December 2018) for its intended purpose and the additional issues were raised:

1/ Impact of UGT2B7 inhibitors: the impact of UGT2B7 inhibitors was further discussed concluding no clinically relevant impact to be expected from UGT2B7 inhibitors on the PK of

mirdametinib. Carboxyl esterases (CES) recombinant phenotyping data were provided suggesting mirdametinib forms an active carboxylic acid metabolite of mirdametinib via CES1. Clinical mass balance data indicate this pathway (forming PD-0315209) contributes 21% to the overall metabolism of mirdametinib, whilst uridine diphosphate glucuronosyltransferase enzymes (UGTs) contributed 50%. Recombinant UGT phenotyping data was used to assess the relative contribution of each UGT and indicated that UGT2B7, UGT1A6, UGT1A1 and UGT1A3 isoforms (fraction metabolised, fmUGT1A1=0.08, fmUGT1A6=0.12, fmUGT2B7=0.21, fmUGT1A3=0.05). The calculation of the highest fraction of mirdametinib metabolized by an individual enzyme, i.e. 21 % (CES 1 or UGT2B7) to ensure that the worst-case scenario in case of inhibition of one individual metabolization pathway was questioned. Detailed calculations for the highest fraction of mirdametinib metabolised by an individual enzyme and for contributions other than UGT and CES were provided. The applicant is recommended to conduct a study with a UGT2B7 inhibitor and a study with a strong CYP3A4 inducer (that also induces UGTs, P glycoprotein [P-gp], and CES enzymes (REC).

In addition, the inter-individual PK variability of mirdametinib was discussed, the additional results from the time-varying covariate analysis of comedication use performed, the results from the exposure-response modelling analysis and finally a PBPK modelling analysis.

Exposure-safety analyses demonstrated exposure-related increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) for grade >1 AE's (not enough events for the analysis of grade >2 events). This relationship is significant for the exposure to mirdametinib as to metabolite PD-0315209, more specific to the steady state AUC from dosing to 12 hours post dose (AUC0-12, ss). Similar relationship is observed for increases in CPK and exposure to mirdametinib (AUC0-12, ss). The AUC0-12, ss for PD-0315209 also shows a significant relationship with the occurrence of acneiform rash AE's (grade >1). No other relationships (for example: ocular toxicity) were observed. A possible increase of 21% in mirdametinib exposure (due to concomitant use of a UGT2B7 or CES inhibitor) would not be considered impactful. However, to evaluate the extend of increase in exposure with UGT2B7 inhibition and provide interpretation in context of the overall safety profile and therapeutic window of mirdametinib, the applicant is recommended to conduct a dedicated study with probenecid as a probe UGT2B7 inhibitor in the post-marketing setting **(REC**).

2/ Impact of UGT2B7 inducers: the impact of a decrease of 21% in mirdametinib exposure resulting from concomitant use of a UGT2B7 inducer was discussed. The clinical mass balance data indicate this pathway (forming PD-0315209) contributes 21% to the overall metabolism of mirdametinib, whilst uridine diphosphate glucuronosyltransferase enzymes (UGTs) contributed 50% that can potentially be induced trough the same mechanism. Furthermore, involvement of other inducing CYP enzymes in mirdametinib metabolism and transporter (P-gP) through the same mechanism cannot be ruled out based on in vitro data (e.g. CYP3A4 and CYP2C). In addition, as previously highlighted, the PBPK platform used to support is considered not sufficiently qualified according to the Guideline on the reporting of PBPK modelling and simulation for its intended purpose. Consequently, from an efficacy perspective, a clinical study with inducers is expected given that it is unlikely that the applicant would have enough data to qualify the PBPK model platform as per the PBPK guideline requirements. The applicant is recommended to conduct a clinical pharmacokinetic trial with a strong CYP3A4 inducer (that also induces UGTs, P-gp, and CES enzymes) with mirdametinib to evaluate the effect of strong CYP3A4 induction on decreasing the systemic exposure of mirdametinib and to provide dosage recommendations for mirdametinib when used concomitantly with strong CYP3A4 inducer (REC). The section 4.5 "Interactions with other medicinal products and other forms of interactions" of the SmPC has been updated accordingly.

The applicant discussed whether the combination with substrates of UGT2B7 and 1A6 (e.g. morphine and paracetamol) may or not impact mirdametinib exposure due to a competitive affinity for these enzymes**.** Such combinations are not expected to have clinically meaningful effect.

The reversible inhibition of mirdametinib and PD-0315209 on CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, have been investigated in the in vitro studies 764-04278, 764-04279, 764-04863, but based on IC50 values rather than the recommended Ki values. The applicant agrees to carry out new in vitro investigations assessing the reversible inhibitory potential of mirdametinib and PD-0315209 on CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP2D6, and CYP3A4 and to estimate their ki values. It is expected that, in line with the ICH M12 guideline (section 7.3.1.), the applicant will address whether the actual unbound concentrations of the drug in the in vitro system are representative to the nominal concentrations for both mirdametinib and PD-0315209 (M15). As part of this procedure, the applicant provided additional information regarding the range of concentrations of mirdametinib and its metabolite PD-0315209 that will be tested in the new in vitro assay planned for assessing the reversible inhibitory potential of mirdametinib and PD-0315209 on CYP2C8, CYP2C9, CYP2C19, CYP1A2, CYP2D6, and CYP3A4 and to estimate their ki values. The 7 concentrations of mirdametinib and PD-0315209 investigated, covered the worst expected concentrations for both mirdametinib and PD-0315209 at systemic level. (REC).

With respect to CYP2B6, the assay has been performed in 2019 according to EU Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2**. The study report indicates that the control substrate has been used at a concentration close to its Km. Consequently, for both mirdametinib (IC50>3,30 µM) and PD-0315209 (IC50> 1 µM), ki is estimated = IC50/2, i.e. 1,15µM and 0,5 µM, respectively. These values are higher the worst estimated at the systemic level for mirdametinib and PD-0315209, 0,195µM and 0,08 µM, respectively. Therefore, no reversible inhibition is expected on CYP2B6 by mirdametinib and PD-0315209.

Results from study 2103064 show no TDI risk was determined as the ratio of shift of percentages of remaining enzyme activity without NADPH over with NADPH preincubation were < 2-fold as defined by the study protocol. However, according to ICH M12, a left shift of the IC50 curve e.g. ≥ 1.5- or 2-fold, from the samples pre-incubated with NADPH compared to those without, suggests a potential for enzyme inactivation by the investigational drug. Whilst no TDI on CYP1A, 2B6, 2C9, 2D6, and 3A4 is expected at therapeutic concentrations, with CYP2C19, the fold-shift ratio for mirdametinib is 1, 63. Even though the applicant provided an additional clarification, it was insufficient to conclude on the lack of TDI effect of mirdametinib at therapeutic concentrations and the applicant is recommended to submit the results of an additional in vitro study according to the ICH M12 Guideline for determining the mirdametinib Ki and Kinact for CYP2C19 (REC).

The inducing potential of mirdametinib has been investigated in three *in vitro* studies. According to the results observed, no inducing effect of mirdametinib at clinically relevant concentrations is expected for CYP1A2 and CY2B6. The CYP3A4 induction data from study C23246 suggest a low potential for CYP3A4 induction at clinically relevant drug concentrations and a minimal risk for clinically relevant CYP3A4 induction. The applicant has reflected the conclusion in the section 5.2 "Pharmacokinetic properties" of the SmPC.

Mirdametinib as a UGT inhibitor has been investigated (study C23255) using recombinant human UGT isoenzymes on UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15. Up to 30µM, mirdametinib did not show any inhibitory effect on these enzymes.

As regards the negative findings, the concentrations tested *in vitro* are well above 50*Cmax,u (0.195 µM and 0.08 µM for mirdametinib and PD-0315209, respectively):

- Study 19SPRWP2 (mirdametinib and PD-0315209 [M15] CYP2B6 inhibition): up to 3.30 µM for mirdametinib (=846 fold*Cmax,u) and up to 1µM for PD-0315209 (=625 fold Cmax,u),

- Study 2103064 (mirdametinib and PD-0315209 [M15] CYP TDI): 10 µM for both mirdametinib and PD-0315209 (=846 fold*Cmax,u and 650*fold Cmax,u for mirdametinib and PD-0315209, respectively),

- Study C23255 (Mirdametinib UGT inhibition): up to 30 µM (=7692 fold*Cmax,u).

The following conclusions are supported at clinically relevant concentrations:

- *In vitro*, mirdametinib and its major metabolite (PD-0315209) is not a CYP2B6 inhibitor.

- *In vitro,* mirdametinib and its major metabolite (PD-0315209) are not time-dependent inhibitors of CYP CYP1A, 2B6, 2C9, 2D6, and 3A4.

-*In vitro,* mirdametinib is not an inhibitor of UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15.

The lower potency of M15, in terms of MEK inhibition, does not preclude a potential inhibitory effect on enzymes/transporters involved in drug elimination. From the ICH M12 Guideline: "If in vitro assessments suggest that the parent drug alone does not inhibit major CYP enzymes/transporters or is not expected to inhibit enzymes/transporters clinically, DDI liability due to metabolites as inhibitors can still exist. As a pragmatic rule, it is recommended to investigate the CYP enzyme and transporter inhibitory potential of metabolites that have total $AUC_{metabolite}$ ≥ 25% of AUC_{parent} and also account for at least 10% of drug-related material in circulation (i.e. considered as a major metabolite, often determined based on radioactivity data)". Hence the EU Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2** recommended to submit the result of a study, investigating the potential inhibitory effect pf PD-0315209 on UGT enzymes in post-marketing setting (REC).

In addition to PD-0315209 (M15), another metabolite of mirdametinib, M22 (a glucuronide metabolite), represented >10% of total radioactivity in plasma (14.7% of total plasma radioactivity). The applicant has not investigated its perpetrator profile arguing that Phase 2 conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation, according to the FDA guidance for safety testing of drug metabolites (2020). This is not agreed. Indeed, in accordance with the ICH M12 Guideline, it is recommended to investigate the CYP enzyme and transporter inhibitory potential of metabolites that have total $AUC_{metabolite}$ ≥ 25% of AUC parent and also account for at least 10% of drug-related material in circulation. The applicant is recommended to investigate the CYP enzyme and transporter inhibitory potential of M22 (REC). The applicant also agreed to include the quantification of M22 concentrations in human plasma in the two planned clinical DDI studies (i.e., CYP3A4 inducer and UGT2B7 inhibitor DDI studies)**.**

"Based on in vitro studies, mirdametinib is a substrate for BCRP and P-gp transporters and its major metabolite is a substrate for BCRP, but such features are unlikely to be clinically relevant (see sections 4.5 and 5.2 of the SmPC).

Neither mirdametinib nor its active metabolite PD-0315209 are substrates of the hepatic uptake transporters OATP1B1 or OATP1B3. Therefore, the combination of mirdametinib with drugs known to inhibit these transporters are not expected to be clinically meaningful.

The applicant did not investigate the ability of mirdametinib and PD-0315209 to be substrates of the renal efflux transporters, MATE1, MATE2K, and the renal uptake transporters, OAT1, OAT3 and OCT2. The renal clearance of mirdametinib and its major metabolite is low (< 25% of the systemic clearance) hence it is agreed that such studies are not warranted.

In vitro studies suggest that mirdametinib and its major metabolite do not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 or MATE2K transporters at clinically relevant concentrations.

In vivo

Studies to assess the DDI potential with combined oral contraceptives (OC) have not been conducted. Mirdametinib is a CYP3A4 inducer but this effect is not expected to be significant at therapeutic concentrations. However, the applicant performed PBPK modelling and simulation to support the lack of DDI liability, both for UGT-related DDI (as a victim) and for CYP-related DDI (as a perpetrator). The qualification of the platform is a prerequisite before accepting predictions as a key source of evidence in high regulatory impact applications. The information provided in the report are not considered sufficient to qualify the platform for UGT or CYP3A4 related DDI. The uncertainty related to the model prediction is not considered sufficiently characterized and considering the embryotoxicity and teratogenicity effects of mirdametinib, and uncertainties on the lack of impact of mirdametinib on systemically acting hormonal contraceptives, this study is warranted. The applicant committed to conduct a dedicated clinical drug-drug interaction study assessing the effect of mirdametinib on oral contraceptives PK in the post-marketing setting (REC). Use of an additional barrier method should be recommended to women using systemically acting hormonal contraceptives (see sections 4.5 and 4.6 of the SmPC).

No clinical DDI study has been conducted with proton-pump inhibitors or H2-antagonists. The combination of mirdametinib with proton-pump inhibitors, antacids, or H2-receptor antagonists is not expected to be clinically meaningful as mirdametinib does not exhibit pH dependent dissolution. Ezmekly can be used concomitantly with gastric pH modifying agents (i.e., H2-receptor antagonists and proton pump inhibitors) without restrictions.

Clinical pharmacodynamic

Secondary pharmacology

▪ Thorough QT study (TQT)

The applicant performed a Thorough QT (TQT) analysis from the study MEK-NF-102: a phase 1, double blind, randomised, 4-treatment, 4-period crossover design. The objective was to assess the effects of mirdametinib and its major metabolite (PD-0315209) on cardiac repolarisation, with a particular focus on QT/QTc prolongation. The study involved four treatment groups comprising healthy adults. Each group received a different treatment: moxifloxacin (positive control), placebo, mirdametinib 6 mg and 14 mg, with a 7-day washout period between each. The 6 mg and 14 mg doses of mirdametinib were selected to represent both therapeutic and supratherapeutic exposures. The primary objective was to measure the adjusted Fridericia-corrected QTc difference (QTcF) after oral administration of mirdametinib, and to compare these values with placebo in order to test for clinically significant QTc prolongations.

The results showed that, at the maximum concentrations following 6 mg and 14 mg dose (i.e. 431 ng/mL, and 1160 ng/mL, respectively), mirdametinib did not have any significant QTc prolongation effect, with the upper limit of the 90% confidence interval consistently remaining below 10 ms. It should be reminded that, according to ICH E14 guidelines, a confidence interval of more than 10 ms could represent a significant prolongation, and therefore a clinical risk. Mirdametinib and its main metabolite had no apparent clinically relevant impact on cardiac repolarisation. The analyses of central tendency, outliers and diagnostic statements were all consistent with the conclusion that there was no

clinically significant effect following the administration of mirdametinib at supratherapeutic exposures. The sensitivity of the assay for a QTc effect for moxifloxacin was successfully achieved.

In conclusion, at the expected maximal therapeutic concentrations, mirdametinib is not expected to prolong the QTc interval and the TQT can be deemed as negative. While there were no clinically significant effects on other ECG parameters (HR, PR, and QRS), mirdametinib was associated with an increase in PR interval and a transient increase in QRS, likely due to a blockade of calcium/sodium currents. This study has been performed using a single dose of mirdametinib. From the TQT study, the applicant discussed the extrapolation of the outcomes on thorough QT observed with two high single doses of mirdametinib, 6 mg and 14 mg, to multiples doses of mirdametinib. However, even though the TQT study showed negative results, it remains not set up for to explore the potential of a QTc shortening effect by mirdametinib and then, its resulting clinical translation in the intended indication cannot be predicted yet.

The likelihood of a drug-drug interaction that would yield significant increases in exposure beyond what has been studied in the TQT study is unlikely given the different metabolic pathways involved in mirdametinib metabolism, and would therefore not be expected to have a clinically meaningful effect in terms of safety or efficacy of mirdametinib at the recommended therapeutic dose.

Outcomes from the pivotal studies

In the pivotal study MEK-NF-201, in the adult cohort, several patients had QTcF between 450 and 480 msec throughout the study, and 1 patient had a QTcF > 480 msec on Cycle 5 Day 15. One TEAE of Grade 1 electrocardiogram 'QT prolonged' was reported. This patient did not report a QTcF > 450 msec.

Overall, the most commonly reported cardiac event was "ejection fraction decreased", occurring in 26.8% of paediatric patients on a dose dependent manner, which is quite significant and of concern, and 16% of adults.

Cardiac conduction effects were reported in 4 (7.1%) paediatric patients and 7 (12.1%) adult patients. Events reported in 2 patients each included supraventricular tachycardia, tachycardia, and ventricular extrasystoles. Other events reported in 1 patient each included electrocardiogram QRS complex prolonged, electrocardiogram QT prolonged, electrocardiogram ST-T segment abnormal, electrocardiogram repolarization abnormality, arrhythmia supraventricular, bradycardia, bundle branch block right, and conduction disorder.

Additionally, in patients with advanced cancer (studies A4581001 and A4581002), 4 patients > 65 years of age, of which 3 patients ≥ 80 years of age, had congestive heart failure. Even if these adverse events may result from confounding factors, they could also be subsequent to the complex electrophysiologic properties of mirdametinib and/or its metabolite. The shortening of the PR interval in the TQT study can result from tachycardia. However, the decrease of the ejection fraction, the enlargement of the QRS and the congestive heart failure in some patients may well be caused by sodium/calcium channel blockade exerted by the drug/metabolite, and the ventricular rhythm problems to the paradoxical enhancing effect of the metabolite on hERG, provided that these patients are sensitized by genetic or other subclinical disorders apart from their neurofibromatosis.

The applicant has clarified that the potential risk of proarrhythmia with mirdametinib pertaining to its potential to prolong the QT/QTc interval, by significantly interacting with potassium channels, has adequately been addressed by in vitro (human ether-a-go-go-related gene [hERG], Purkinje) and in vivo (cardiovascular monkey) studies. The applicant clarified mirdametinib's effect on the cardiac contractile function providing clinical and non-clinical argumentation. However, mirdametinib's impact on sodium channels and L-type calcium channels remains unclear. The evaluation of Vmax as provided by the applicant is not considered sensitive enough and the applicant is requested to further

investigate the effect of mirdametinib and metabolite on sodium channels and L-type calcium channels by heterologous expression systems, such studies as transfected human sodium and calcium channels in mammalian cell system. The applicant committed to conduct a dedicated in vitro assay (**REC**).

The decrease in ejection fraction is an important identified risk in the risk management plan. However, available studies demonstrated that mirdametinib interacts with calcium and sodium channels at concentrations close to intended therapeutic concentrations. These channels are involved in cardiac contractibility and conduction, and may be related to clinical effects observed, i.e. decrease of left ejection fraction, bundle branch block. Hence, an additional important potential risk of adverse effects on cardiac conduction was added to the list of the safety concerns in the RMP.

Furthermore, although no risk was identified on QT prolongation (hERG or clinical study), it is important to keep in mind that we are in rare situation that the metabolite of mirdametinib could participate to a gain of hERG function if sufficient exposition is achieved, with yet unclear clinical consequences.

Influence of food

A food effect on mirdametinib PK was demonstrated. With a high fat meal, Cmax decreased by 43% and AUCinf by 7% (data not shown). However the decreased Cmax with food is not considered clinically relevant, since Cmax level has no effect on efficacy nor safety.

Therefore the currently proposed recommendation in section 4.2 that mirdametinib can be taken with or without food is considered acceptable.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics, pharmacodynamic and drug-drug interaction profile of mirdametinib and its metabolite M15 are considered sufficiently characterised and the relevant information has been included in sections 4.5 and 5.2 of the SmPC. However, a number of aspects pertaining to DDI aspects, and the PK characterization of the disproportionate metabolite M30 which has been unreliably considered, as a minor metabolite are expected to be investigated post-approval as Recommendations (RECs).

2.6.5. Clinical efficacy

Table 10: Summary of mirdametinib clinical studies assessing efficacy

Study Identifier/ Status/Sponsor	Study Title	Dosing Regimen	Number of Participants Exposed to Mirdametinib
MEK-NF-201/ Ongoing/SpringWorks	A Phase 2b Trial of the MEK inhibitor mirdametinib (PD-0325901) in Patients with NF1-Associated PN	28-day cycles, intermittent doses: 2 mg/m^2 BID with a maximum of 4 mg BID on a 3 week on/1 week off schedule	58 Adults (≥18 years) 56 Paediatrics (2 to <18 years)

Study Identifier/ Status/Sponsor	Study Title	Dosing Regimen	Number of Participants Exposed to Mirdametinib
NF-106/Completed/IIR	A Phase 2 Trial of the MEK Inhibitor mirdametinib (PD-0325901) in Adolescents and Adults with NF1-Associated Plexiform Neurofibromas	28-day cycles, intermittent doses: 2 mg/m^2 BID with a maximum of 4 mg BID on a 3 week on/1 week off schedule	17 Adults (≥18 years) 2 Paediatrics (16 to <18 years)

Abbreviations: BID: twice daily; IIR: investigator-initiated research; MEK: mitogen-activated protein kinase kinase; NF1: neurofibromatosis type 1; PN: plexiform neurofibromas.

This application is based on an ongoing single open-label, single arm, multi-centre phase I/II study in adult and paediatric participants with NF1-Associated Plexiform Neurofibromas.

The applicant also provided the result of a completed phase II study in adult and adolescent participants with NF1-Associated Plexiform Neurofibromas.

Additionally, the applicant used as external control data from participants included in the placebo arm of a tipifarnib study (01 C-0222) and from a Natural History non interventional prospective study (08-C-0079).

2.6.5.1. Dose response study(ies)

The applicant did not conduct dose response studies, the rationale for the chosen dose is based on clinical data from previous studies in patients with advance cancers and on non-clinical data showing that the plasma concentrations that resulted in a tumour volume reduction in 85% of mice in a NF1 mouse model were similar to the plasma concentrations obtained in adults at the 2 mg BID dose. See the Dose rationale paragraph in section 2.6.2.1. Pharmacokinetics.

2.6.5.2. Main study

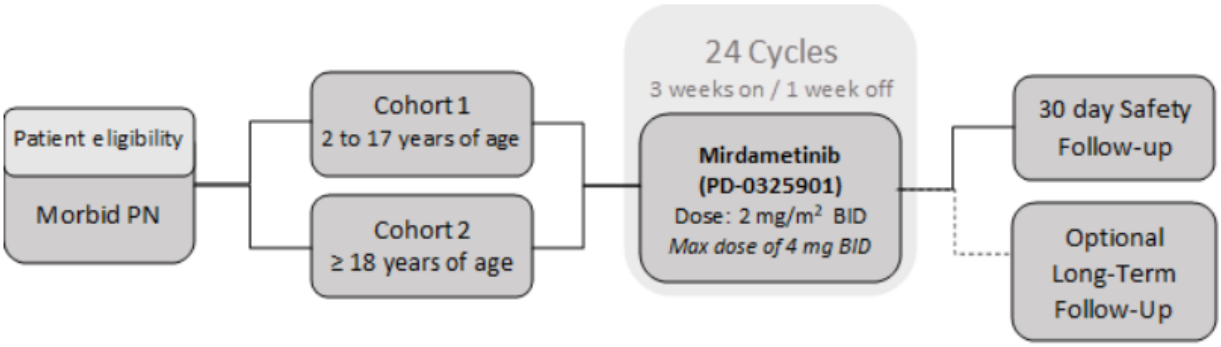
MEK-NF-201: A Phase 2b Trial of the MEK 1/2 Inhibitor PD-0325901 in Adult and Paediatric Patients with Neurofibromatosis Type 1-Associated Inoperable Plexiform Neurofibromas that are Causing Significant Morbidity

Methods

MEK-NF-201 (ReNeu) is an ongoing open-label, multi-centre, phase IIb study being conducted to determine the efficacy and safety of mirdametinib (PD-0325901) in participants ≥ 2 years old with an inoperable NF1-associated PN causing significant morbidity.

This study consists of two phases: the Treatment Phase and the optional Long-Term Follow-Up (LTFU) Phase; the LTFU Phase is currently ongoing.

Figure 14: Study schema



- **Study Participants**

Main inclusion criteria

Age:

- Participant must have been ≥ 2 years of age inclusive.

Type of participant and disease characteristics

- Participants must have had EITHER the clinical diagnosis of NF1 using the National Institute of Health (NIH) Consensus Conference criteria of at least 1 other diagnostic criterion in addition to the presence of PN, OR have a constitutional NF1 mutation documented in a Clinical Laboratory Improvement Amendments/College of American Pathologists certified lab; additional criteria are as follows:
    - Six or more café-au-lait macules with a diameter > 5 mm in pre-pubertal and > 15 mm in post-pubertal individuals, respectively
    - Freckling in axilla or inguinal regions
    - Optic glioma
    - Two or more Lisch nodules
    - A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia of thinning of long bone cortex)
    - A first degree relative with NF1.
- Participants must have had a target PN that was causing significant morbidity, such as (but not limited to) head and neck lesions that were compromising the airway or great vessels, brachial or lumbar plexus lesions that were causing nerve compression and loss of function, lesions causing major deformity or were significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Histologic confirmation of tumour was not necessary in the presence of consistent clinical and radiographic findings but should have been considered if malignant degeneration of a PN was clinically suspected.
- Participant had a target PN that was deemed inoperable, defined as a PN that cannot be completely surgically removed without risk for substantial morbidity due to: encasement of or close proximity to vital structures, invasiveness, or high vascularity of the PN, or the participant refuses surgery. Participants who previously underwent surgery for a PN were eligible to enter the study after the surgery, provided the PN was incompletely resected and was evaluable by volumetric analysis.

- Participants must have had a target PN, defined as the clinically most relevant PN, amenable to volumetric MRI analysis. For the purpose of this study, the target PN must have been seen on at least 3 consecutive MRI slices and the field of view must have contained the entire tumour of interest. As determined by central radiologic review, a target PN must have been analysable by volumetric using the REiNS criteria, at least 5 mL in volume, and was classified as "typical PN", "nodular PN", or "solitary nodular PN" prior to first dose of study treatment.

- Participants ≥ 16 years of age must have had a Karnofsky performance level of ≥ 50%, and participants < 16 years must have had a Lansky performance level of ≥ 50%.

- Participant had adequate organ and bone marrow function

- Participant must have weighed at least 10 kg, inclusive

- Participant must have had a BSA of at least 0.4 m^2 (inclusive) calculated using the Du Bois formula (BSA = 0.007184 × W0.425 × H0.725).

Main exclusion criteria

Medical Conditions

- Participant had a screening alanine transaminase (ALT) value of > 2.0xULN, total bilirubin value of > 1.5x ULN (isolated bilirubin > 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).

- Participant had a history of malignancy associated hypercalcemia.

- Participant had an active parathyroid disorder, hyperphosphatemia at screening.

- Any clinically significant active or known history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

- Participants with evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy.

- Participant had abnormal QT interval corrected by Fridericia's formula (> 450 msec for male participants, > 470 msec for female participants, or > 480 msec for participants with bundle branch

- Participant had experienced any of the following within 6 months (24 weeks): clinically significant cardiac disease, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism.

- Participant had recorded a left ventricular ejection fraction (LVEF) < 55% at screening or within 3 years of signing informed consent/assent, OR had a history of congestive heart failure.

- Participant had a history of, or evidence of, retinal pathology on ophthalmologic examination that was considered a risk factor for central serous retinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration. Participants were excluded from study participation if they had any of the following risk factors for RVO at screening:

o Intraocular pressure > 21 mmHg

o Serum cholesterol > 300 mg/dL

o Serum triglycerides > 300 mg/dL

o Hyperglycaemia (fasting blood glucose > 125 mg/dL or random blood glucose > 200 mg/dL)

o Participants ≥ 13 years of age with a blood pressure ≥ 140/90 mm Hg

o Participants ≤ 12 years of age with a blood pressure ≥ 95th percentile for age + 12 mmHg

- Participant had a history of glaucoma.

Prior/Concomitant Therapy

o Participant had received NF1 PN-targeted therapy (e.g. farnesyltransferase inhibitors, kinase inhibitors, etc.) within 45 days of first dose of study treatment (or 5.5 half-lives, whichever was longer).

o Participant previously received or was currently receiving therapy with mirdametinib or any other MEK1/2 inhibitor (e.g. selumetinib, trametinib, cobimetinib, binimetinib, etc.).

o Participant was receiving systemic, inhaled, or ocular glucocorticoid therapy (with the exception of participants with endocrine deficiencies who are allowed to receive physiologic or stress doses of steroids, if necessary) within 14 days prior to first dose of study treatment.

o Participant had received radiation therapy within the 6 months prior to signing of informed consent/assent

- **Treatments**

The study treatment consisted of mirdametinib 1 mg and 2 mg capsules and 0.5 mg and 1 mg tablets.

All participants self-administered the study treatment at a dose of 2 mg/m^2 BID (approximately every 12 hours without regard to food), utilizing an intermittent (3-weeks on/1-week off) dosing schedule in 28-day cycles.

Dosing was based on different nomograms specific for tablets or capsules, irrespectively of age. These two nomograms were used to allow for smaller increments in dose with the tablet, as this formulation is available in unit dose strengths of 0.5 mg and 1 mg whereas the capsule formulation is only available in unit dose strengths of 1 mg and 2 mg.

In the initial protocol only the capsule formulation was available, the tablet formulation was introduced during amendment 2 (June 2020). However, the applicant did not apply for a marketing authorisation for the 0.5 mg tablet formulation.

Table 11: Study Treatment Dosing

Capsule dosage form [1]

BSA (m^2)	0.4 to 0.69	0.7 to 1.04	1.05 to 1.49	≥ 1.5
BID unit dose	1 mg	2 mg	3 mg	4 mg

BSA = body surface area; mg = milligrams
All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

Dispersible tablet dosage form (paediatric formulation)[1]

BSA (m^2)	0.4 to 0.59	0.6 to 0.79	0.8 to 0.99	1 to 1.39	1.4 to 1.59	1.6 to 1.69	≥ 1.7
BID unit dose	1 mg	1.5 mg	2 mg	2.5 mg	3 mg	3.5 mg	4 mg

BSA = body surface area; mg = milligrams
All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

1 The dispersible tablet formulation (paediatric formulation) is available in 0.5 mg increments whereas the capsule formulation is only available in 1 mg increments. Therefore, while the approximate total dose per BSA (2 mg/m2) is the same regardless of formulation, the unit dose per BSA may vary between formulations.

In the event of significant toxicity, dosing was interrupted and/or dose reduced as described in Table 12 and Table 13.

Table 12: Criteria For dose modification for study drug-related adverse events

RELATED ADVERSE EVENTS	INTERVENTION
OCULAR/VISUAL	
Any Grade ≤ 2 event.	Continue dosing and perform ophthalmologic exams every 2 to 4 weeks until resolution to Grade ≤ 1 or baseline.
Any Grade ≥ 3 event except RVO.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Table 13. Consider ophthalmologic exams every 2 to 4 weeks.
Grade ≥ 3 retinal vein occlusion (RVO).	Permanently discontinue study treatment.
NEUROLOGICAL	
Grade ≤ 2 events such as hallucination, confusion or delirium lasting more than 24 hours AND after ruling out other possible causes.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Table 13.
Any Grade ≥ 3 event.	Withhold dose and discuss with the Medical Monitor. Consider permanent discontinuation after re-evaluating the benefit risk of ongoing study drug treatment.
MUSCULOSKELETAL	
Grade ≥ 3 muscle weakness (symptomatic and interfering with ADL).	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Table 13
DERMATOLOGICAL	
Grade ≥ 3 acneiform rash.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose following Table 13.
CARDIAC	
Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of ≤10% from baseline and is below institutional lower limit of normal (LLN).	Interrupt dosing; if LVEF value improves to above the institutional LLN or baseline, resume at the same dose, if supported by the investigator's assessment of the benefit-risk ratio. If LVEF does not improve to above the institutional LLN or baseline within 14 days, permanently discontinue study treatment.

RELATED ADVERSE EVENTS	INTERVENTION
Asymptomatic, absolute reduction in LVEF of > 10% to ≤ 19% from baseline and is below institutional lower limit of normal (LLN).	Interrupt dosing; if LVEF value improves to above the institutional LLN or baseline within 14 days, resume at the next lower dose level following Table 13. If LVEF does not improve to above the institutional LLN or baseline within 14 days, permanently discontinue study treatment.
Symptomatic congestive heart failure. Absolute decrease in LVEF of greater than 20% from baseline.	Permanently discontinue study treatment.
OTHER	
Grade ≥ 3 hematologic toxicities or clinically significant Grade 2 hematologic abnormalities that do not resolve within 72 hours after initiation of medical management.	Interrupt dosing; if resolution to Grade ≤ 1 occurs within 14 days, restart study treatment at the next lower dose following Table 13.
Grade ≥ 3 nonhematologic toxicity that is not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose following Table 13.
Other Grade 2 toxicity that is subjectively intolerable (except alopecia) and not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the same dose.
Recurrent subjectively intolerable toxicity (at least a week interruption on 2 occasions) that is not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose using Table 13. If toxicity is still intolerable, permanently discontinue study treatment (unless otherwise discussed with the Medical Monitor or Sponsor).

Table 13: Dose reduction

Capsule dosage form

Dose at the time of the event	Reduced dose
1 mg BID	1 mg AM
2 mg BID	2 mg AM; 1 mg PM
3 mg BID	2 mg BID
4 mg BID	3 mg BID

BID = twice daily; mg= milligrams

Capsule dosage form dose modification nomogram

BSA (m2)	0.4 to 0.69	0.7 to 1.04	1.05 to 1.49	≥ 1.5
Modified Dose	1 mg AM	2 mg AM, 1 mg PM	2 mg BID	3 mg BID

BID = twice daily; BSA = body surface area; mg = milligrams
All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

Dispersible tablet dosage form (paediatric formulation)

Dose at the time of the event	Reduced dose
1 mg BID	1 mg AM; 0.5 mg PM
1.5 mg BID	1 mg BID
2 mg BID	1.5 mg BID
2.5 mg BID	2 mg AM; 1.5 mg PM
3 mg BID	2.5 mg AM; 2 mg PM
3.5 mg BID	2.5 mg BID
4 mg BID	3 mg AM; 2.5 mg PM

BID = twice daily; mg= milligrams

Dispersible tablet dosage form (paediatric formulation) dose modification nomogram

BSA (m^2)	0.4 to 0.59	0.6 to 0.79	0.8 to 0.99	1 to 1.39	1.4 to 1.59	1.6 to 1.69	≥ 1.7
Modified Dose	1 mg AM, 0.5 mg PM	1 mg BID	1.5 mg BID	2 mg AM, 1.5 mg PM	2.5 mg AM, 2 mg PM	2.5 mg BID	3 mg AM, 2.5 mg PM

BID = twice daily; BSA = body surface area; mg = milligrams
All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

- **Objective and outcomes/endpoints**

The primary endpoint was defined as the percentage of patients with complete response (CR) or confirmed partial response (PR), with PR defined as target Plexiform Neurofibroma (PN) volume decrease ≥20% at the end of the Treatment Phase compared to baseline. Responses were considered confirmed if the PR was maintained at the subsequent MRI within the 2 to 6 months. Evolution in target PN volume compared to baseline was assessed by a blinded independent central reviewer (BICR) in order to minimize investigator bias.

The secondary endpoints included the duration of response (DoR), evaluation of pain intensity assessed with the Numerical Rating Scale-11 (NRS-11) and of pain interference measured by the Pain Interference Index (PII).

The secondary and tertiary endpoints covered a wide range of clinical outcomes, as symptoms may vary based on the location and extent of PN.

Table 14: Summary of estimand (Study MEK-NF-201)

Estimand Attribute	Description
Primary Efficacy Estimand – Confirmed Objective Response Rate	
Population	Participants ≥2 years old. Paediatric and adult cohorts were analysed separately.
Treatment condition	Mirdametinib administered orally at a dose 2 mg/m^2 BID (maximum dose of 4 mg BID) on a 3 weeks on/1 week off schedule.
Endpoint	Confirmed ORR at the end of the Treatment Phase (defined as PN decrease ≥20% compared to baseline in consecutive scans within 2-6 months) using centrally read MRI volumetric analysis.
Population-level summary	The proportion of participants who have a confirmed objective response at the end of the Treatment Phase, calculated separately by age cohort. Exact 2-sided Clopper-Pearson 95% CIs were calculated on the confirmed objective response rate.
Intercurrent events	Permanent discontinuation of study treatment Strategy: Treatment policy strategy, participants who permanently discontinued from the Treatment Phase before the Cycle 24 visit were required to return to the clinic for an early termination visit as close as possible to the last dose of study treatment (mirdametinib). Participants were also required to return for a Safety Follow-Up visit (30 days [+5 days] after the last dose of study drug). Disease Progression Strategy: While-on-treatment strategy, data before event were assessed to determine confirmed objective response status. Death Strategy: While-on-treatment strategy, data before event were assessed to determine confirmed objective response status. Subsequent Anticancer Therapy Strategy: Treatment policy strategy, data before and after event were considered to determine confirmed objective response status.
Secondary Efficacy Estimand – Duration of Response	
Population	Participants ≥2 years old, who meet the criteria for confirmed ORR. Paediatric and Adult cohorts were also analysed separately.
Treatment condition	Mirdametinib administered orally at a dose 2 mg/m^2 BID (maximum dose of 4 mg BID) on a 3 weeks on/1 week off schedule.
Endpoint	Duration of response for participants whose best overall confirmed response was complete response or partial response using centrally read MRI volumetric analysis. Duration of response is defined as the time between the first instance of response that is subsequently confirmed and the date of radiographic disease progression or death, whichever occurs first.
Population-level summary	The median duration of response using the Kaplan-Meier method and corresponding 95% CIs.

Estimand Attribute	Description
Intercurrent events	Permanent discontinuation of study treatment Strategy: Treatment policy strategy, participants who permanently discontinued from the Treatment Phase before the Cycle 24 visit were required to return to the clinic for an early termination visit as close as possible to the last dose of study treatment (mirdametinib). Participants were also required to return for a Safety Follow-Up visit (30 days [+5 days] after the last dose of study drug). Disease Progression Strategy: Composite strategy, part of endpoint definition. Death Strategy: Composite strategy, part of endpoint definition. Surgery impacting the target PN or start subsequent systemic therapy for the treatment of PNs Strategy: Alternative therapy impacting the target PN was prohibited and would have caused the user to withdraw from study. The participant was censored at the last adequate tumour assessment before target PN surgery or subsequent PN treatment (While-on-treatment strategy).

Abbreviations: BID: twice daily; MRI: magnetic resonance imaging; NRS-11: Numeric Rating Scale-11; ORR: objective response rate; PedsQL: Paediatric Quality of Life Inventory; PII: Pain Interference Index; PN: plexiform neurofibroma.

- **Sample size**

The planned sample size of 100 enrolled participants were stratified by age, with 50 participants aged 2 to 17 years for the paediatric cohort and 50 participants ≥ 18 years of age for the adult cohort.

It was projected that an observed ORR of at least 42% (at least 21 objective responses) in 50 treated adult participants would result in a lower bound of the 95% confidence interval (CI) that excludes 28%. This was considered evidence of clinically significant activity of mirdametinib. This was equivalent to testing a null ORR rate of 23% compared to a target rate of 43% with 80% power and 2-sided alpha of 0.05. Similarly, an observed ORR of 64% (at least 32 objective responses) in 50 treated paediatric participants would result in a lower bound of the 95% CI that excludes 49%.

For the analysis of safety, there was a 95% chance of observing at least 1 adverse event (AE) that occurs at an underlying rate of 3.0% in a sample size of 100 participants.

The assumptions for the response rate in the adult population used for the basis of sample size estimation were based on the study conducted by Weiss et al. (Weiss 2021). The preliminary results from this study describe an ORR (as defined by a 20% reduction by of the target lesion from baseline) of 42% (95% CI: 20% to 67%) in response to one year of mirdametinib therapy.

The results of tumour response post-therapy at > 1 year had not yet been released. This finding was consistent with the preliminary data of cabozantinib in patients with a morbid or progressing PN. In a phase II study of cabozantinib in adults > 16 years of age with an evaluable PN, 8 of 19 patients achieved an objective response (42%) (Shih et al. 2018).

Sample size assumptions for the paediatric population were based on the interim results from the SPRINT study conducted by Gross et al. (Gross 2018). The SPRINT study enrolled 50 patients aged 3-18 years with inoperable morbid PNs. At the time, this study had demonstrated a confirmed ORR of 68%. The hypothesis testing was updated following the release of the ORR based on independent central review (ICR) from the SPRINT study (44%[8]). These findings were consistent with the preliminary data of another PN study with trametinib. Twenty-six participants aged 1 to 17 years of

[8] Multi-disciplinary Review and Evaluation NDA 213756, Koselugo (selumetinib), version July 24, 2019

age (median 5.5 years) with a measurable PN were treated with trametinib for a median of 61 weeks (range 3 to 124 weeks). In this study, 12 participants (46%) achieved an objective response.

- **Randomisation and blinding (masking)**

This was an open-label, single arm study. Randomisation and blinding to study treatment are therefore not applicable in this study.

A blinded independent central review (BICR) was used for the primary endpoint adjudication and analysis.

- **Statistical methods**

Analysis population

Full Analysis Set (FAS): defined as the set of all participants who received at least one dose of mirdametinib. The efficacy endpoints were based on the FAS.

Per-Protocol Set (PPS): defined as the set of all participants in the FAS who had completed at least one post-baseline disease evaluation and who did not have any major CSR reportable deviations, including but not limited to efficacy assessments or compliance. The PPS was used in a supportive analysis of confirmed ORR.

Safety Analysis Set: defined as the set of all participants who took at least one dose of study treatment. The Safety Analysis Set was used for all safety analyses.

Primary endpoint

The primary efficacy endpoint of interest was the confirmed ORR by the end of Treatment Phase (i.e. Cycle 24). The confirmed ORR was defined as the proportion of participants who had a ≥ 20% reduction in target tumour volume as compared to baseline as assessed by a BICR. The response needed to be confirmed in a consecutive tumour assessment within 2-6 months during the Treatment Phase. The best overall confirmed response (CR, PR, SD, PD, NE – where SD/PD/NE only required a singular response to be deemed confirmed at that level) per participant was summarized as defined below:

- CR (complete response): A complete resolution of the target PN
- PR (partial response): A ≥ 20% reduction in the volume of the target PN lesion compared to baseline
- SD (stable disease): Between a < 20% increase and < 20% decrease in the volume of the target PN lesion compared to baseline
- PD (progressive disease): A ≥ 20% increase in the volume of the target PN compared to baseline
- NE: not evaluable.

All tumour volume measurements were independently calculated by two BICR readers. In case the two readers' generated measurements represent different categorical tumour response statuses, an independent adjudicator made the final decision on which reader's assessment was the best representation of the tumour response and the selected response category was recorded at that visit. The primary endpoint analyses were performed using the adjudicator-selected reader for those visits where the two BICR readers did not agree.

Only tumour assessments during the Treatment Phase were considered for the determination of confirmed response. Participants who did not achieve a confirmed response were categorized as non-responders. Participants who did not have a post-baseline MRI assessment were also categorized as non-responders and their best overall response was deemed as 'Missing'.

To assess the primary efficacy endpoint, confirmed ORRs by the end of the Treatment Phase as assessed by BICR was presented as a percentage alongside the corresponding 2-sided 95% Clopper-Pearson CIs and the p-values from one-sample two-sided binomial tests for the confirmed ORR compared to the minimum clinically relevant response rates (23% in adult participants and 20% in paediatric participants). The overall assessment of the endpoint was based on the exclusion of the minimum clinically relevant response rates by the lower tail of the 95% CIs.

Sensitivity analysis

A sensitivity analysis was performed that mirrored this primary efficacy analysis but used the PPS set rather than the FAS.

As additional sensitivity analyses, the confirmed ORR was summarized by each central BICR reader separately for both the FAS and the PPS.

Secondary endpoints

Duration of Response (DoR)

DoR was defined as the time in months between the first instance of response that was subsequently confirmed, until the date of radiographic disease progression or death, whichever occurred first. The DoR was summarized in months as follows: (date of event [i.e. radiographic disease progression or death] or censoring – date of first response + 1) / 365.25 × 12.

For participants who entered the LTFU Phase, all MRI assessments in both the Treatment Phase and LTFU Phase were used to determine DoR. Those who achieved a DoR of at least 12 months were considered to have experienced a durable response.

Participants without radiographic disease progression or death while on study had their results censored to their most recent adequate (i.e. evaluable) tumour assessment date.

Table 15: Censoring and event rules for DoR

Situation	Date of Censoring or Event	Outcome
No adequate tumor assessment post confirmed response	Date of tumor assessment that resulted in response confirmation	Censored
No radiographic disease progression or death post confirmed response	Date of last adequate tumor assessment	Censored
New surgery or subsequent anticancer PN therapy started prior to radiographic disease progression post confirmed response	Date of last adequate tumor assessment before the start of new therapy or surgery	Censored
Two or more consecutive missing or non-adequate tumor assessments post confirmed response	Date of last adequate tumor assessment before the first missing or non-adequate assessment	Censored
Radiographic disease progression that has been verified by BICR post confirmed response	Date of the earliest tumor assessment that results in a finding of progression	Event
Death before radiographic disease progression post confirmed response	Date of death	Event

DoR was analysed using Kaplan-Meier (KM) methods, with the median, lower, and upper quartile estimates of DoR and their associated 95% CI using the Brookmeyer and Crowley method.

Sensitivity analysis for DoR

The MEK-NF-201 protocol defined PD as an "increase in the volume of the target lesion by 20% or more compared to baseline". However, the REiNS criteria (Dombi et al. 2013) define PD as an "increase in the volume of the target lesion by 20% or more compared to baseline or the time of best response after documenting a PR." To assess the durability of the response using a similar criterion to REiNS, the following sensitivity analyses were performed using the PN volume from the two central readers, separately by each reader:

• DoR applying the REiNS criteria using all scans (i.e. considering scans from both the Treatment Phase and the LTFU Phase); defined as the time from the first response that was subsequently confirmed to the derived disease progression scan using BICR PN volume data or death. That is, if a participant had an early confirmed response, a subsequent increase of at least 20% from the confirmed response would not necessarily have been considered as PD at that time point. For example, if the participant had MRI scans showing an even larger shrinkage in target PN volume at later scans, then the largest target PN shrinkage at the later time point would have been considered the best response when determining PD according to the REiNS criteria.

• DoR applying REiNS using real-time review; defined as the time from first response that was subsequently confirmed to the derived disease progression scan using BICR PN volume data or death considering only the scans up to and including each visit, to assess PD in a real-time review. That is, if a participant had an early confirmed response, a subsequent increase of at least 20% from the confirmed response would have been considered as PD at that time point, regardless of if the participant had MRI scans showing an even larger shrinkage in target PN volume at later scans.

PRO analyses

All PROs analysed in this study were assessed using the mean change from baseline as well as the proportion of participants who achieved a clinically meaningful change from baseline at the Cycle 13 visit. Cycle 13 was selected as the time point that will best allow the treatment effect to be captured in PRO scores. It was projected that a strong majority of participants who present a response would do so at or before Cycle 13, with the median time of response expected to be Cycle 5 to Cycle 9, so any associated pain or QoL improvements should be captured at the Cycle 13 visit. Choosing a later cycle would have captured few additional responses and may have been susceptible to increased amounts of missing data.

Participants and/or proxies used an ePRO device to complete the NRS-11 and PII assessments in a home setting prior to specified clinic visits, depending on participant age at time of consent. NRS-11, PII, PGIC, PGIS and PROMIS assessments were completed at clinic visits, as applicable on the ePRO device. The reason for missing an assessment by the participant (e.g. refusal, device issue etc.) was not captured on the ePRO home device nor in the clinical database and is therefore unknown in all cases. ePRO completion compliance was monitored throughout the study and mitigation strategies were implemented.

The PedsQL was completed by participant and/or proxy on paper at specified clinic visits and the reason it was not completed was captured in the clinical database. This information is included in the completion rate tables and listings.

For PedsQL, NRS-11, and PII, a meaningful change threshold (MCT), or meaningful score difference (Food and Drug Administration [FDA] 2023), was derived by anchor-based analysis of the study's data, where feasible. Additionally, meaningful score change differences were also analysed using distribution-based thresholds. The primary focus of these analyses was identifying if a relevant difference existed at Cycle 13.

Paediatric Quality of Life Inventory

PedsQL items were answered on a Likert scale with responses ranging from 0 to 4. These items were then reverse scored and linearly transformed to a 0-100 scale as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0, with higher scores indicating better outcomes. Overall subscale scores were calculated as the mean of the scores for the questions in each specific subscale (or of all questions for total score).

Anchor-based and distribution-based MCTs were applied to interpret the change from baseline results as well as the number and percentage of participants with a clinically meaningful change for PedsQL. Distribution-based thresholds were 0.5*standard deviation (StD), where StD was calculated from the baseline Scale Score data. MCTs were defined separately for adult, paediatric self-report, and paediatric parent proxy data.

Numeric Rating Scale (NRS)-11

Participants were asked to select the one number from 0 to 10 that best described their worst pain over the past 24 hours for target tumour pain with 0 representing "no pain" and 10 representing "worst pain you can imagine." The NRS-11 score presented at each visit was taken as the average of the responses over the 7 consecutive days up to and including visit day, with no transformation applied.

Anchor-based and distribution-based MCTs were applied to interpret the change from baseline results as well as the number and percentage of participants with a clinically meaningful change for NRS-11. Distribution-based thresholds were presented using change from baseline of ≤ -1, representing a clinically meaningful improvement, as well as change from baseline greater than the within-patient MCT.

Pain Interference Index (PII)

The PII consists of 6 questions, each asking the responder to select one number from 0 to 6 that best describes how their/their child's pain has impacted various items over the past 24 hours with 0 representing "Not at all" and 6 representing "Completely". The mean of the completed items was taken as the PII score for a single assessment. The PII score presented at each visit was taken as the average of the PII scores over the 7 consecutive days up to and including visit day, with no transformation applied.

Anchor-based and distribution-based MCTs were applied to interpret the change from baseline results as well as the number and percentage of participants with a clinically meaningful change for PI. Distribution-based thresholds were < -0.5*StD (using StD from the baseline scores).

PRO statistical analyses

Actual values and change from baseline were descriptively summarized for each age cohort by visit, for participants overall and by confirmed objective response status.

The number and percentage of participants with a change representing a clinically meaningful improvement (as described above, alongside associated 95% Clopper-Pearson CIs) were also presented, within each age cohort, and in the subgroup of participants who have a confirmed objective response status versus the subgroup of those who do not. The differences in the proportions of participants reaching the anchor-based/distribution thresholds between responders and non-responders was tested using a Chi-Square test at a 5% significance level.

For a given PRO endpoint, a Mixed Model for Repeated Measures (MMRM) was fitted separately by age cohort. The change from baseline was the dependent variable, the visit was fitted as a fixed effect, and the baseline value used as a covariate. Covariance structures were to be trialled in the order of decreasing complexity, with the first structure that converges without error used. The structures tested were as follows: Unstructured, Heterogenous Toeplitz, Heterogenous Autoregressive, Autoregressive, Heterogenous Compound Symmetry, Compound Symmetry, Variance Components. A Kenward-Roger approximation will be used for the degrees of freedom. This model was to be fitted twice, once using only data through Cycle 13, and once including data from the entire study (time points with < 5 subjects would not be presented).

Additionally, a sensitivity analysis was performed using imputed data. In this analysis, monotone missing data (i.e. in situations where no subsequent values are available) were considered missing not at random (MNAR) and imputed to the subject's baseline value (no improvement nor worsening from baseline).

Multiplicity adjustment

The primary efficacy endpoint was assessed separately for each age cohort. The lower limit of the 95% confidence interval for the primary endpoint was compared to a minimal clinically relevant response in the age groups.

Changes to planned analyses

The first patient enrolled was on 21 October 2019. The data cut-off date for the final study report was 20 September 2023.

Changes in planned analyses introduced in protocol amendments

The following aspects of the planned analyses were modified after first patient first visit as part of protocol global amendments.

Table 16: Changes in planned analyses introduced in protocol amendments

Protocol version	Changes to the planned analyses
Amendment 2 (5 June 2020)	Sample size determination was updated to provide clarity on the trial statistical assumptions for the paediatric and adult strata.
Amendment 3 (14 June 2021)	Analysis set populations were clarified to align with a single-arm study analysis.
Amendment 4 (17 May 2022)	Sample size determination text was simplified to clarify sample size required for analysis and remove redundancies. Text was added to clearly state the independent analysis of the paediatric and adult cohorts. To this end, the use of 'strata/stratum' was changed to 'cohort' to reflect the independence of populations The confidence interval for the primary efficacy analysis was updated to reflect hypothesis testing and clarified handling of data from discontinued participants.

Changes in the planned analyses introduced in the statistical analysis plan

Two draft versions of the SAP dated 20 September 2022 and 31 January 2023 were submitted to FDA for review and feedback. The final SAP (v1.0.0) was approved on 03 November 2023.

The key assumption of the sample size and associated clinically relevant ORR was the claimed ORR of 66% from the selumetinib SPRINT study. During study conduct, the applicant became aware that the ORR based on independent central review from the SPRINT study was 44%.

As per the meeting minutes of the Type C meeting with FDA conducted on 16 November 2022, the confirmed ORR was assessed primarily by the exclusion of a minimum clinically relevant rate using the lower bound of the 95% CI. The SAP was updated to specify the type of CI as a 95% Clopper-Pearson CI.

In addition, as per the meeting minutes of the Type C meeting with FDA conducted on 16 November 2022, the assessment of tumour volume according to MRI was performed independently by two readers and, in the case of the two readings yielding different categorical tumour response status, an independent adjudicator made the final determination of response category as per SAP. Thus, further clarification was added to the SAP regarding adjudication, as well as including sensitivity analyses by each of the two independent readers.

As suggested by the FDA, a specific time point was fixed for the analysis of PROs. In this study, Cycle 13 was considered as the time of interest for all PRO analysis. This update was described in the SAP. This was accompanied by the specification of a meaningful score difference used in the analysis of secondary PROs. Additionally, an anchor-based analysis of PROs was performed; this was detailed fully in a separate MCT analysis plan (Version 1.0, dated 12 September 2023).

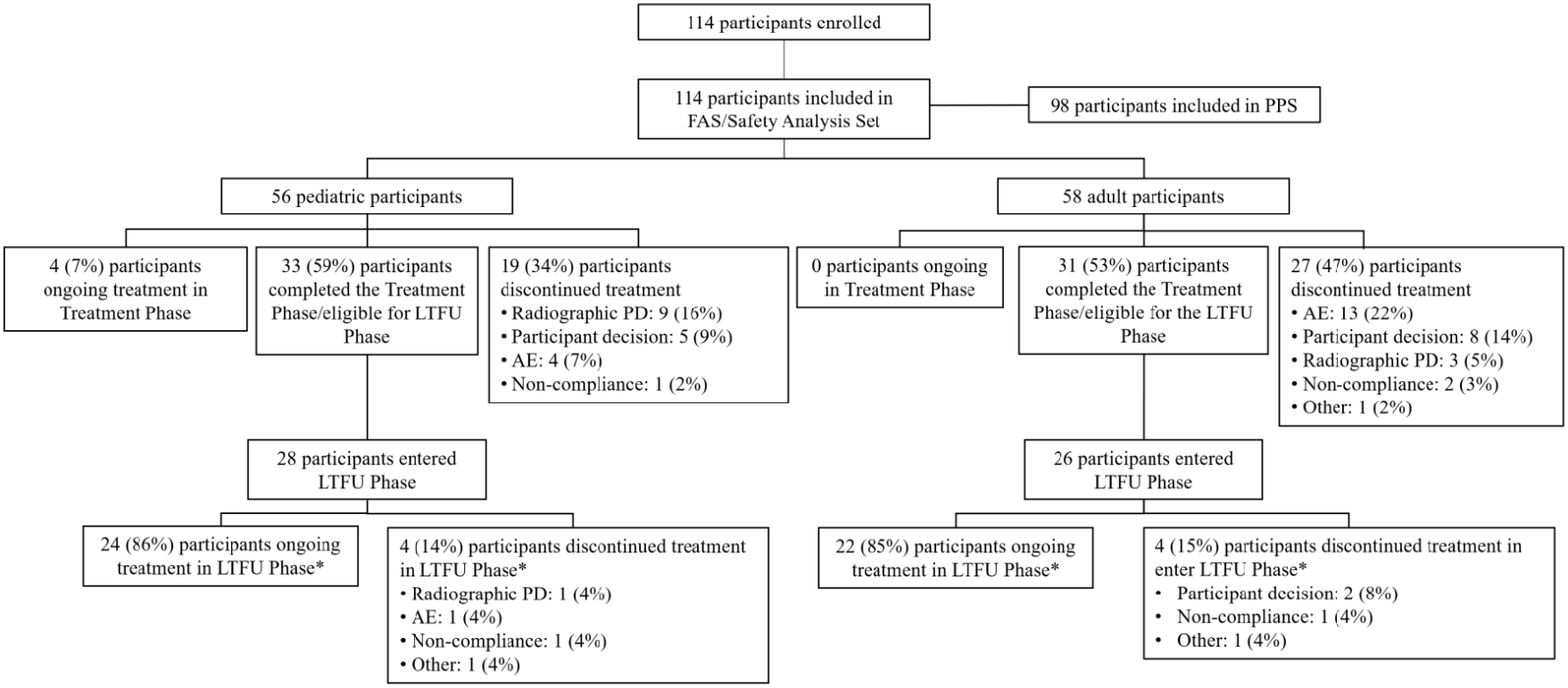
Following the Type C meeting with FDA on 16 November 2022, the planned analysis of historical controls data was expanded. A separate SAP was produced as an addendum to the main SAP to provide full details of the expanded historical controls data analysis (SAP Addendum). The use of a balancing model, (e.g. propensity score matching) was considered for the comparisons for the TTP and PFS endpoints between the paediatric cohort, and the NF1 natural history study and placebo arm from the prior clinical trial of tipifarnib (Widemann et al. 2014).

Results

Unless otherwise specified, the results presented in this section are the 20 September 2023 DCO of the primary CSR.

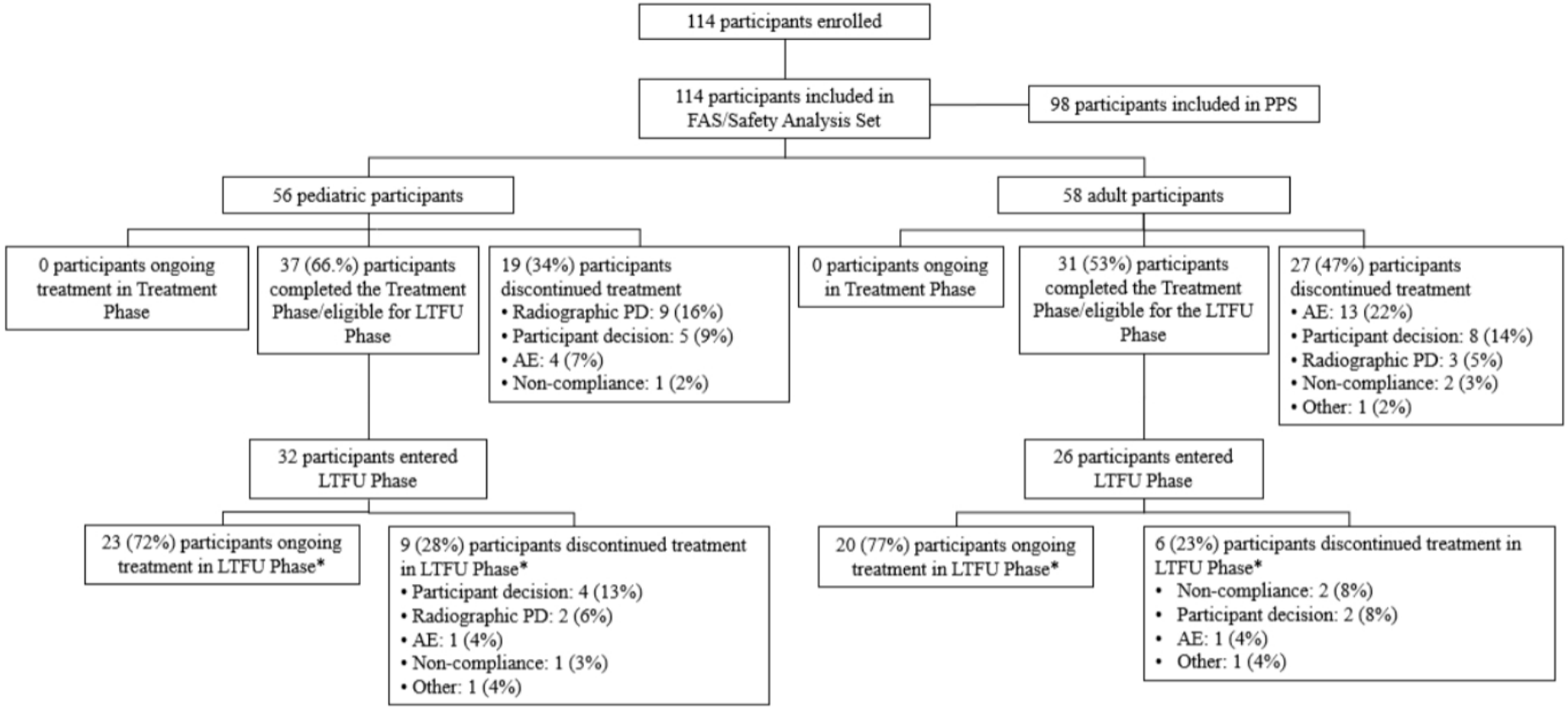
- **Participant flow**

Figure 15: Disposition of patients (Enrolled Set)



Abbreviations: AE: adverse event; FAS: Full Analysis Set; LTFU: long-term follow-up; PD: progressive disease; PPS: Per Protocol Set.

* Percentages were calculated out of the number of participants eligible for LTFU Phase. Figure 16. Disposition of Patients (Enrolled Set)


114 participants enrolled
114 participants included in FAS/Safety Analysis Set
98 participants included in PPS
56 pediatric participants
58 adult participants
0 participants ongoing treatment in Treatment Phase
37 (66.%) participants completed the Treatment Phase/eligible for LTFU Phase
19 (34%) participants discontinued treatment
• Radiographic PD: 9 (16%)
• Participant decision: 5 (9%)
• AE: 4 (7%)
• Non-compliance: 1 (2%)
0 participants ongoing in Treatment Phase
31 (53%) participants completed the Treatment Phase/eligible for the LTFU Phase
27 (47%) participants discontinued treatment
• AE: 13 (22%)
• Participant decision: 8 (14%)
• Radiographic PD: 3 (5%)
• Non-compliance: 2 (3%)
• Other: 1 (2%)
32 participants entered LTFU Phase
26 participants entered LTFU Phase
23 (72%) participants ongoing treatment in LTFU Phase*
9 (28%) participants discontinued treatment in LTFU Phase*
• Participant decision: 4 (13%)
• Radiographic PD: 2 (6%)
• AE: 1 (4%)
• Non-compliance: 1 (3%)
• Other: 1 (4%)
20 (77%) participants ongoing treatment in LTFU Phase*
6 (23%) participants discontinued treatment in LTFU Phase*
• Non-compliance: 2 (8%)
• Participant decision: 2 (8%)
• AE: 1 (4%)
• Other: 1 (4%)

- **Recruitment**

First participant enrolled: 21 October 2019

Data cut-off date: 20 September 2023.

The study enrolled 114 participants in 50 sites across the United States.

- **Conduct of the study**

Amendment 1 (17 May 2019)

A total of 63 participants were initially consented under Protocol Amendment 1, which included the following major changes:

- A safety run-in cohort was added to the paediatric stratum (stratum 1).
- Changed the MRC grading assessment from option to a required strength assessment.
- The 6-minute walk test was added as an assessment for participants that have a target PN causing airway or lower extremity motor dysfunction.
- The entry criterion based on progression of target PN was removed and any associated instruction or language pertaining to a progressing target PN prior to study entry.

Amendment 2 (05 June 2020)

A total of 110 participants were initially consented under Protocol Amendment 2, which included the following major changes:

• The tablet formulation was added along with general guidance for this formulation.

• Inclusion Criteria #5 was updated to clarify that the tumour assessment is based on the REiNS criteria.

• Exclusion Criteria #16 and #17 were modified to clarify that previous treatment with a MEK inhibitor at any time was not allowed.

• Dose modifications in response to an ocular AE were updated to align with current MEK inhibitor class guidance.

• Sample size determination was updated to provide clarity on the trial statistical assumptions for the paediatric and adult strata.

Amendment 3 (14 June 2021)

In addition to the planned protocol amendment, a protocol-mandated screening and enrolment hold was placed on 07 May 2021 due to a participant reported Grade 3 event of RVO. A safety evaluation was completed by SpringWorks and reviewed with the data monitoring committee.

After a thorough risk-benefit assessment, screening and enrolment were resumed on 20 May 2021. There were no changes to study treatment for enrolled participants during the screening and enrolment hold.

A total of 14 participants were initially consented under Protocol Amendment 3, which included the following major changes:

• The LTFU Phase and LTFU Phase-specific Schedule of Assessment were added to the protocol.

• Exclusion Criterion #18 was modified to explicitly exclude inhaled glucocorticoid therapy.

Amendment 4 (17 May 2022)

No participants were initially consented under Protocol Amendment 4, which included the following major changes:

• The P-OMAQ was added as an exploratory endpoint for participants ≥ 8 years and caregivers of all participants and incorporated as a single administration PRO to assess acceptability of the tablet (paediatric formulation).

• The confidence interval for the primary efficacy analysis was updated to reflect hypothesis testing and clarified handling of data from discontinued participants.

Protocol deviations

In the paediatric cohort, 3 (5%) participants had at least 1 major protocol deviation and were therefore excluded from the PPS. These deviations included study eligibility; 1 participant did not meet inclusion criterion #5 (their target PN volume at baseline was < 5 mL) and 2 participants did not meet inclusion criterion #3 (reported no morbidity at baseline) and both were enrolled in the study.

In the adult cohort, 6 (10%) participants had at least 1 major protocol deviation and were therefore excluded from the PPS. These deviations included study inclusion (2 [3%] participants; both participants did not meet inclusion criterion #5 and were enrolled in the study with baseline target PN volumes measured < 5 mL) and investigational product (4 [7%] participants; all 4 participants received < 60% prescribed study treatment during the Treatment Phase).

- **Baseline data**

Table 17: Summary of demography and baseline characteristics (FAS)

	Paediatric	Adult	Total
	(N = 56)	(N = 58)	(N = 114)
Age at time of consent (years)			
n	56	58	114
Mean (StD)	10.1 (4.50)	35.0 (13.17)	22.8 (15.94)
Median	10.0	34.5	18.0
Min, Max	2, 17	18, 69	2, 69
2 to < 12 years	32 (57.1%)	N/A	32 (28.1%)
12 to < 18	24 (42.9%)	N/A	24 (21.1%)
Sex			
Male	26 (46.4%)	21 (36.2%)	47 (41.2%)
Female	30 (53.6%)	37 (63.8%)	67 (58.8%)
Childbearing Potential at Screening			
Yes	15 (50.0%)	29 (78.4%)	44 (65.7%)
No	15 (50.0%)	8 (21.6%)	23 (34.3%)
Race			
Black or African American	11 (19.6%)	5 (8.6%)	16 (14.0%)
White	37 (66.1%)	49 (84.5%)	86 (75.4%)
Asian	2 (3.6%)	2 (3.4%)	4 (3.5%)
American Indian or Alaska Native	1 (1.8%)	0	1 (0.9%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5 (8.9%)	2 (3.4%)	7 (6.1%)

	Paediatric	Adult	Total
Ethnicity			
Hispanic or Latino	8 (14.3%)	1 (1.7%)	9 (7.9%)
Not Hispanic or Latino	44 (78.6%)	52 (89.7%)	96 (84.2%)
Missing/Not Reported/Unknown	4 (7.1%)	5 (8.6%)	9 (7.9%)
Karnofsky/Lansky Score			
n	56	58	114
Mean (StD)	94.5 (9.33)	87.1 (7.73)	90.7 (9.29)
Median	100.0	90.0	90.0
Min, Max	50, 100	70, 100	50, 100

Abbreviations: FAS: Full Analysis Set; Max: maximum; Min: minimum; StD: standard deviation. N represents the number of participants in the corresponding cohort.
Childbearing potential percentages were calculated using the number of female participants in the corresponding cohort as the denominator.
The Karnofsky Performance Status scores range from 0 to 100. A higher score means the participant was better able to carry out daily activities.

Table 18: Summary of baseline disease characteristics (FAS)

	Paediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Target Tumour Location			
Head & Neck	28 (50.0%)	28 (48.3%)	56 (49.1%)
Lower Extremities	4 (7.1%)	15 (25.9%)	19 (16.7%)
Other	8 (14.3%)	3 (5.2%)	11 (9.6%)
Paraspinal	4 (7.1%)	5 (8.6%)	9 (7.9%)
Chest Wall	2 (3.6%)	4 (6.9%)	6 (5.3%)
Mesentery & Pelvis	5 (8.9%)	1 (1.7%)	6 (5.3%)
Upper Extremities	4 (7.1%)	2 (3.4%)	6 (5.3%)
Abdominal Wall	1 (1.8%)	0	1 (0.9%)
Target Tumour Type (Reader A)[a]			
Nodular	11 (19.6%)	15 (25.9%)	26 (22.8%)
Solitary Nodular	2 (3.6%)	4 (6.9%)	6 (5.3%)
Typical	43 (76.8%)	39 (67.2%)	82 (71.9%)
Time Since Target PN Diagnosis (Months)			
n	42	22	64
Mean (StD)	55.97 (50.714)	157.45 (169.241)	90.85 (116.540)
Median	42.96	82.83	59.35
Min, Max	2.0, 183.0	3.0, 598.5	2.0, 598.5
Documented NF1 Mutation (CLIA/COA testing)			
Yes	25 (44.6%)	27 (46.6%)	52 (45.6%)
No	19 (33.9%)	18 (31.0%)	37 (32.5%)
Unknown	12 (21.4%)	13 (22.4%)	25 (21.9%)
Target PN Progressing at Study Entry			
Yes	35 (62.5%)	31 (53.4%)	66 (57.9%)
No	21 (37.5%)	27 (46.6%)	48 (42.1%)
Any Reported Morbidities			
Motor Dysfunction or Weakness	15 (26.8%)	23 (39.7%)	38 (33.3%)
In Lower Extremity	10 (17.9%)	15 (25.9%)	25 (21.9%)
In Upper Extremity	5 (8.9%)	8 (13.8%)	13 (11.4%)
Airway Dysfunction	7 (12.5%)	3 (5.2%)	10 (8.8%)

	Paediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Pain	39 (69.6%)	52 (89.7%)	91 (79.8%)
Disfigurement or Major Deformity	28 (50.0%)	30 (51.7%)	58 (50.9%)
Other	12 (21.4%)	10 (17.2%)	22 (19.3%)
Optic Glioma			
Yes	16 (28.6%)	11 (19.0%)	27 (23.7%)
No	40 (71.4%)	47 (81.0%)	87 (76.3%)
Prior PN Treatments			
Yes	8 (14.3%)	11 (19.0%)	19 (16.7%)
No	48 (85.7%)	47 (81.0%)	95 (83.3%)
Prior PN Surgery			
Yes	20 (35.7%)	40 (69.0%)	60 (52.6%)
No	36 (64.3%)	18 (31.0%)	54 (47.4%)
Prior PN Radiotherapy			
Yes	0	1 (1.7%)	1 (0.9%)
No	56 (100%)	57 (98.3%)	113 (99.1%)

Abbreviations: CLIA: Clinical Laboratory Improvement Amendments; COA: Certificate of Accreditation; NF1: neurofibromatosis type 1; PN: plexiform neurofibroma; StD: standard deviation.
N represents the number of participants in the corresponding cohort.
Percentages were calculated using the number of participants in the corresponding cohort as the denominator.
Morbidities were not mutually exclusive; a participant may have had more than one reported morbidity.
Optic glioma was not a reason for enrolment in the study and was not assessed on study for changes to treatment.
Note: The exclusion criteria were modified in Protocol Amendment 2 to not allow prior MEK inhibitors.
Time since target PN diagnosis (in months) was calculated as (treatment start date – diagnosis date) × 12 / 365.25.
a Target tumour type was only categorized by Reader A.

Prior therapies

A total of 25 (45%) participants in the paediatric cohort had at least 1 prior PN therapy: 8 (14%) had targeted medications/therapies, and 20 (36%) had surgery. Six (11%) participants had received prior MEK inhibitor therapy; the most common prior PN targeted medications were selumetinib and trametinib.

A total of 43 (74%) participants in the adult cohort had at least 1 prior PN therapy: 11 (19%) had targeted medications/therapies, 1 (2%) had radiation therapy, and 40 (69%) had. Four (7%) participants had received prior MEK inhibitor therapy; the most common (> 2 participants) prior PN medication was selumetinib.

Table 19: Summary of participants who reported prior MEK inhibitor therapy

Participant Number	Medication	Start Date	Stop Date	Dose	Best Overall Response on Prior Therapy	Reason for Treatment Discontinuation on Prior Therapy
Paediatric						
	Cobimetinib	02 Nov 2016	13 Dec 2017	20-40 mg	SD	Disease progression
	Trametinib	02 Feb 2016	01 Nov 2017	1 mg	PD	Disease progression
	Selumetinib	10 May 2018	29 Apr 2020	80 mg	Not reported	Toxicity

	Selumetinib	29 Jul 2019	11 Jul 2020	45 mg	SD	Toxicity
	Trametinib	28 Feb 2018	22 Mar 2019	0.5 mg	PR	Other: pain re-emerged, escalated dose
	Trametinib	23 Mar 2019	30 Apr 2020	0.5 alternating with 1 mg	SD	Other: PN pain, wanted to participate in trial
	Trametinib	07 Oct 2016	24 Oct 2016	2 mg	SD	Completed therapy
	Trametinib	31 Oct 2016	14 Feb 2020	1 mg	SD	Completed therapy
	Selumetinib	14 Jun 2018	12 Feb 2020	20 mg	SD	Disease progression
Adult						
	MEK inhibitor	31 Dec 2013	31 Dec 2013	Unknown	PD	Disease progression
	Selumetinib	16 Mar 2019	17 Jul 2019	90 mg	NE	Toxicity
	Selumetinib	11 Apr 2016	31 Aug 2019	50 mg	NE	Other: patient decision to withdraw
	Selumetinib	01 May 2018	18 Sep 2019	50 mg BID	SD	Other: patient decision

Abbreviations: BID: twice daily; MEK: mitogen-activated protein kinase; NE: not evaluable; PD: progressive disease; PN: plexiform neurofibroma; PR: partial response; SD: stable disease.

Numbers analysed

Table 20: Summary of participant disposition by cohort – treatment phase (enrolled set) 20 September 2023

	Paediatric (N = 56)	**Adult (N = 58)**	**Total (N = 114)**
Participants in the Safety Analysis Set	56 (100%)	58 (100%)	114 (100%)
Participants in the FAS	56 (100%)	58 (100%)	114 (100%)
Participants in the PPS	51 (91.9%)	47 (81.0%)	98 (86.0%)
Completed the Treatment Phase	33 (58.9%)	31 (53.4%)	64 (56.1%)
Ongoing in the Treatment Phase	4 (7.1%)	0	4 (3.5%)
Discontinued/Withdrawn from Study Prior to Completing the Treatment Phase	19 (33.9%)	27 (46.6%)	46 (40.4%)
Primary Reason for Discontinuation/Withdrawal from Study Prior to Completing the Treatment Phase			
Death	0	1 (1.7%)	1 (0.9%)
Radiographic PD	9 (16.1%)	3 (5.2%)	12 (10.5%)
Withdrawal by participant	3 (5.4%)	0	3 (2.6%)
AE	3 (5.4%)	12 (20.7%)	15 (13.2%)
Participant decision	3 (5.4%)	8 (13.8%)	11 (9.6%)
Lost to follow-up	1 (1.8%)	2 (3.4%)	3 (2.6%)
Other	0	1 (1.7%)	1 (0.9%)

Ongoing Treatment in Treatment Phase	4 (7.1%)	0	4 (3.5%)
Discontinued Treatment Prior to Completing the Treatment Phase	19 (33.9%)	27 (46.6%)	46 (40.4%)
Primary Reason for Discontinuing Treatment Prior to Completing the Treatment Phase			
Radiographic PD	9 (16.1%)	3 (5.2%)	12 (10.5%)
AE	4 (7.1%)	13 (22.4%)	17 (14.9%)
Non-compliance	1 (1.8%)	2 (3.4%)	3 (2.6%)
Participant decision	5 (8.9%)	8 (13.8%)	13 (11.4%)
Other	0	1 (1.7%)	1 (0.9%)
Withdrawing Consent from the Study Prior to Completing the Treatment Phase	3 (5.4%)	0	3 (2.6%)
Reason for Withdrawing Consent from the Study Prior to Completing the Treatment Phase			
Inability or refusal to complete study procedures	1 (1.8%)	0	1 (0.9%)
Intolerable side effects	1 (1.8%)	0	1 (0.9%)
Participant refusal to continue study medication	1 (1.8%)	0	1 (0.9%)
Eligible for LTFU Phase	33 (58.9%)	31 (53.4%)	64 (56.1%)
Entering LTFU Phase	28 (84.8%)	26 (83.9%)	54 (84.4%)
Did Not Enter LTFU phase	5 (15.2%)	5 (16.1%)	10 (15.6%)

Abbreviations: AE: adverse event; FAS: Full Analysis Set; PD: progressive disease; PPS: Per-protocol Set; LTFU: Long-term Follow-up.
Participants were considered to have completed the Treatment Phase if they completed the Cycle 24 visit (End of Treatment Phase) or have entered the LTFU Phase.
The Safety Analysis Set was defined as the set of all participants who took at least one dose of mirdametinib.
The FAS was defined as participants who received at least one dose of mirdametinib.
The PPS was defined as the set of all participants in the FAS who completed at least one post-baseline disease evaluation and who did not have any major CSR-reportable deviations, including but not limited to efficacy assessments or compliance.
N represents the number of enrolled participants in the corresponding cohort.
Percentages were calculated out of the number of participants eligible for LTFU Phase for 'entering LTFU Phase/did not enter LTFU Phase' and reasons for not entering, and out of all participants in the cohort for all other rows

- **Outcomes and estimation**

Primary Endpoint: Confirmed ORR

The confirmed ORR was defined as the proportion of participants who had a confirmed ≥ 20% reduction in target tumour volume compared to baseline as assessed by a BICR. The response needed to be confirmed in a consecutive tumour assessment within 2-6 months. All tumour volume measurements were independently calculated by 2 reviewers.

Table 21: Analysis of confirmed ORR – treatment phase (FAS) data cut-off 20 September 2023

	Paediatric (N = 56)	**Adult (N = 58)**
Confirmed ORR		
n	29	24
ORR %	51.8	41.4
95% CI	(38.0, 65.3)	(28.6, 55.1)
p-value	< 0.001	< 0.001
Best Overall Confirmed Response Status		
CR	0	0

PR	29 (51.8%)	24 (41.4%)
SD	22 (39.3%)	26 (44.8%)
PD	3 (5.4%)	0
Not Evaluable	0	0
Missing	2 (3.6%)	8 (13.8%)

Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; FAS: Full Analysis Set; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.
Target lesion baseline occurred at Screening Visit.
N represents the number of participants in the corresponding cohort. n is the number of confirmed objective responders.
Confirmed objective response was defined as two consecutive assessments of PR or CR assessed by a BICR within 2-6 months during the Treatment Phase.
95% CIs were derived using the Clopper-Pearson approach. p-values were calculated using a one-sample two-sided binomial test compared to the minimally clinically relevant response rates of 23% for the adult cohort and 20% for the paediatric cohort.
Participants who had no post-baseline MRI assessment or no confirmed objective response were treated as non-responders.
Best overall confirmed response status was defined as the best confirmed response prior to disease progression during the Treatment Phase.
Missing contains participants who had no post-baseline assessments.

The applicant provided during the procedure an updated dataset with a longer follow-up.

Updated data (DCO 12 June 2024) provided 9 additional months of follow-up from the primary analysis data cut-off (DCO 20 September 2023):

In the paediatric cohort, 2 additional participants achieved a confirmed PR in the LTFU Phase. Inclusive of these responses, the confirmed ORR (95% CI) in the paediatric cohort was 55.4% (41.5, 68.7)

In the adult cohort, 3 additional participants achieved a confirmed PR in the LTFU Phase. Inclusive of these responses, the confirmed ORR (95% CI) in the adult cohort was 46.6% (33.3, 60.1)).

Secondary Endpoint: DoR

At the primary analysis data cut-off date (20 September 2023), the Kaplan-Meier estimated median DoR was not reached for the paediatric cohort due to no events occurrence; 22 (76%) of paediatric responders were maintaining a confirmed response for at least 12 months, and no disease progression or deaths were observed.

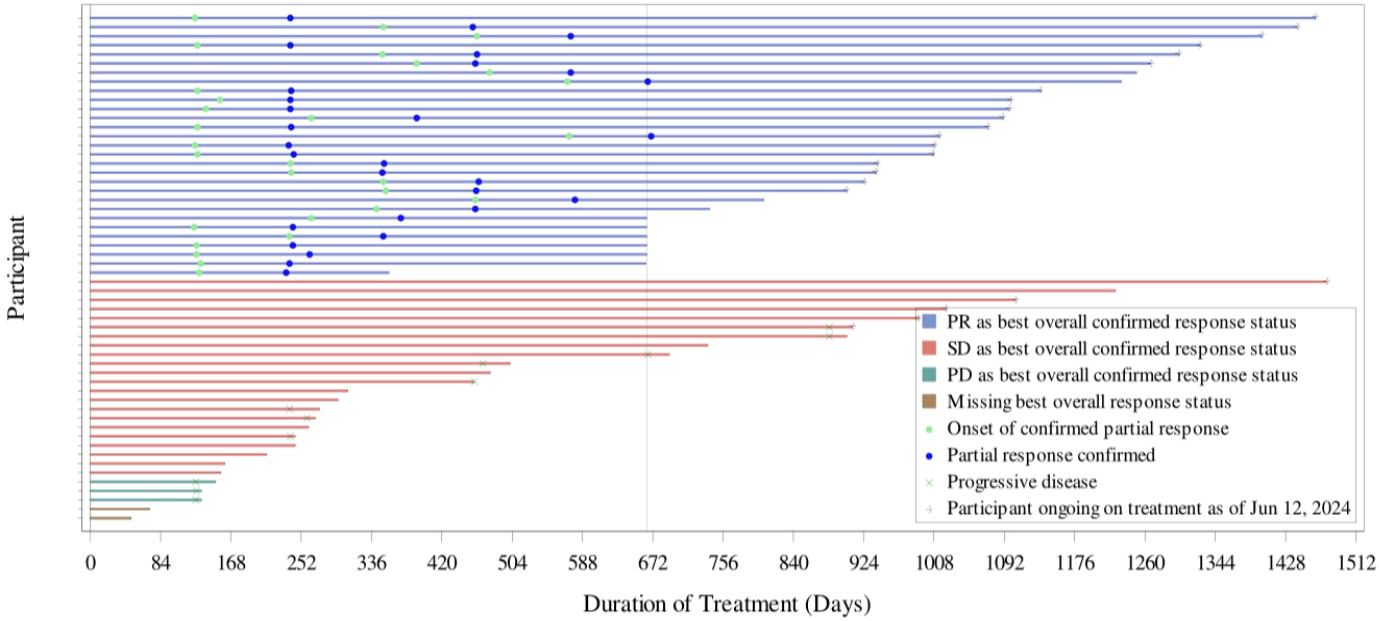
The Kaplan-Meier estimated median DoR was not reached for the adult cohort with only 1 event of PD after achieving a confirmed objective response as of the data cutoff; 18 (75%) of adult responders were maintaining an observed response for at least 12 months; 1 PD and no deaths were observed.

Updated results:

As of 12 June 2024, in the paediatric cohort the Kaplan-Meier estimated median duration of response (DoR) was not reached due to no events (i.e. progressive disease events [PDs] or deaths) and 26 (89.7%) responders maintained a response for ≥12 months.

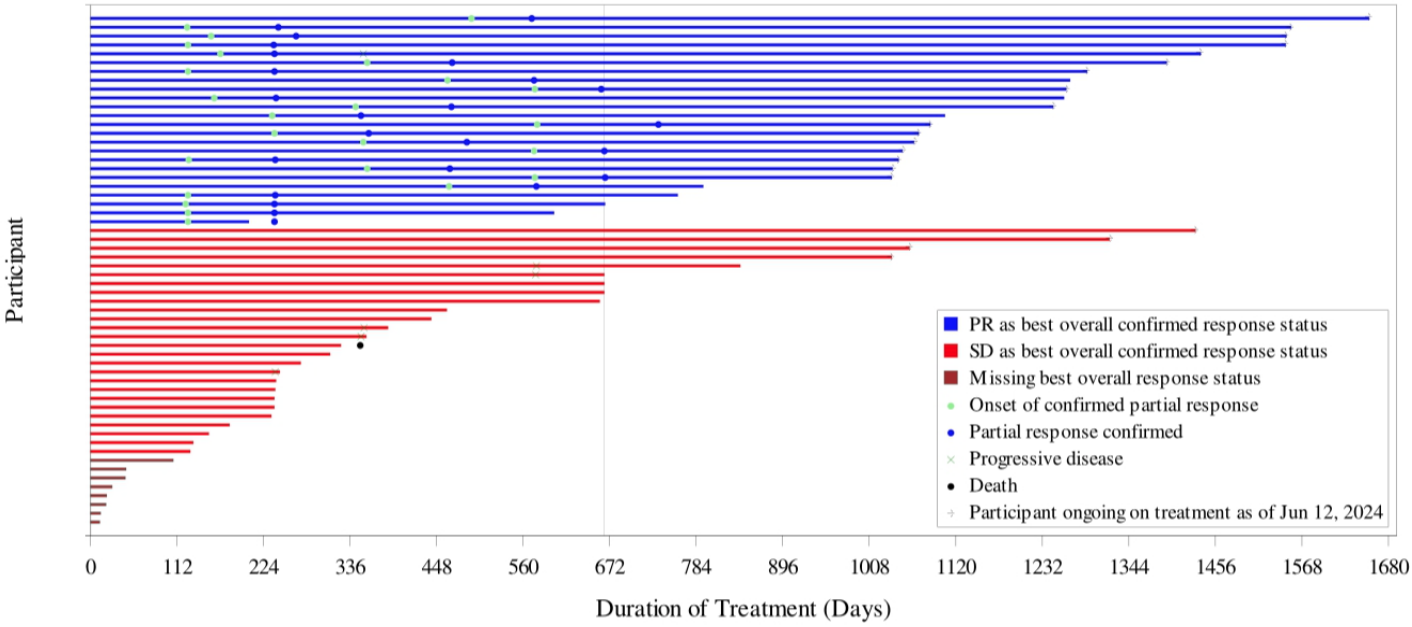
In the adult cohort The Kaplan-Meier estimated median DoR was not reached due to 1 event of PD after achieving a confirmed objective response and 21 (87.5%) responders maintained a response for ≥12 months.

Figure 17: Swimmer plot of duration of treatment (FAS) for participants in the paediatric cohort (DCO 12 June 2024)



Abbreviations: FAS: Full Analysis Set; PD: progressive disease; PR: partial response; SD: stable disease.
The duration of treatment is defined as the time from the date of the first exposure to treatment to the date they discontinued treatment.
Confirmed objective response is defined as two consecutive assessments of PR or CR within 2-6 months, as designated by BICR during the Treatment Phase.
The grey vertical line corresponds to the hypothetical date of the end of Treatment Phase on C24D21 (Day 665), assuming the study visit schedule was followed.

Figure 18: Swimmer plot of duration of treatment (FAS) for participants in the adult cohort (DCO 12 June 2024)



Abbreviations: FAS: Full Analysis Set; PD: progressive disease; PR: partial response; SD: stable disease.
The duration of treatment is defined as the time from the date of the first exposure to treatment to the date they discontinued treatment.
Confirmed objective response is defined as two consecutive assessments of PR or CR within 2-6 months, as designated by BICR during the Treatment Phase.

The grey vertical line corresponds to the hypothetical date of the end of Treatment Phase on C24D21 (Day 665), assuming the study visit schedule was followed.

Table 22: Kaplan-Meier analysis of DoR (Study MEK-NF-201, FAS)

	Primary Analysis (Data Cut-Off 20 Sep 2023)		Update (Data Cut-Off 12 June 2024)	
	Paediatric (N=56)	**Adult (N=58)**	**Paediatric (N=56)**	**Adult (N=58)**
Number of Participants with Confirmed Response	29 (51.8%)	24 (41.4%)	29 (51.8%)	24 (41.4%)
Number of Participant Events	0	1 (4.2%)	0	1 (4.2%)
PD	0	1 (100%)	0	1 (100%)
Death	0	0	0	0
Number of Censored Participants	29 (100%)	23 (95.8%)	29 (100%)	23 (95.8%)
Reason for Censoring				
No Adequate Tumour Assessment Post Confirmed Response	1 (3.4%)	3 (13.0%)	0	1 (4.3%)
No PD/Death Post Response Confirmation	27 (93.1%)	20 (87.0%)	27 (93.1%)	22 (95.7%)
Underwent PN Therapy/Surgery Prior to PD/Death	1 (3.4%)	0	2 (6.9%)	0
Two or More Consecutive Missing/Non-Adequate Assessments	0	0	0	0
Duration of Response (Months)				
1st Quartile	NE	NE	NE	NE
95% CI	(NE, NE)	(6.1, NE)	(NE, NE)	(6.1, NE)
Median	NE	NE	NE	NE
95% CI	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
At 12 Months				
Number of Events Experienced by This Point	0	1 (4.2%)	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	22 (75.9%)	18 (75.0%)	26 (89.7%)	21 (87.5%)
Kaplan-Meier Response Rate Estimate	1.00	0.95	1.00	0.96
95% CI	(1.00, 1.00)	(0.71, 0.99)	(1.00, 1.00)	(0.73, 0.99)
At 24 Months				
Number of Events Experienced by This Point	0	1 (4.2%)	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	4 (13.8%)	9 (37.5%)	14 (48.3%)	12 (50.0%)

	Primary Analysis (Data Cut-Off 20 Sep 2023)		Update (Data Cut-Off 12 June 2024)	
	Paediatric (N=56)	**Adult (N=58)**	**Paediatric (N=56)**	**Adult (N=58)**
Kaplan-Meier Response Rate Estimate	1.00	0.95	1.00	0.96
95% CI	(1.00, 1.00)	(0.71, 0.99)	(1.00, 1.00)	(0.73, 0.99)

Abbreviations: BICR: blinded independent central review; CR: complete response; CSR: clinical study report; DoR: duration of response; FAS: Full Analysis Set; NE: not evaluable; PD: progressive disease; PN: plexiform neurofibroma; PR: partial response.

DoR was defined as the time in months between that first instance of response that was subsequently confirmed, until the date of radiographic disease progression or death, whichever occurred first.

Confirmed objective response was defined as consecutive assessments of PR or CR within 2 to 6 months as designated by BICR during the Treatment Phase.

Percentages were calculated out of the number of participants with a confirmed response for the number with PD/censored, number of events experienced by this point, and number of participants still event-free by this point.

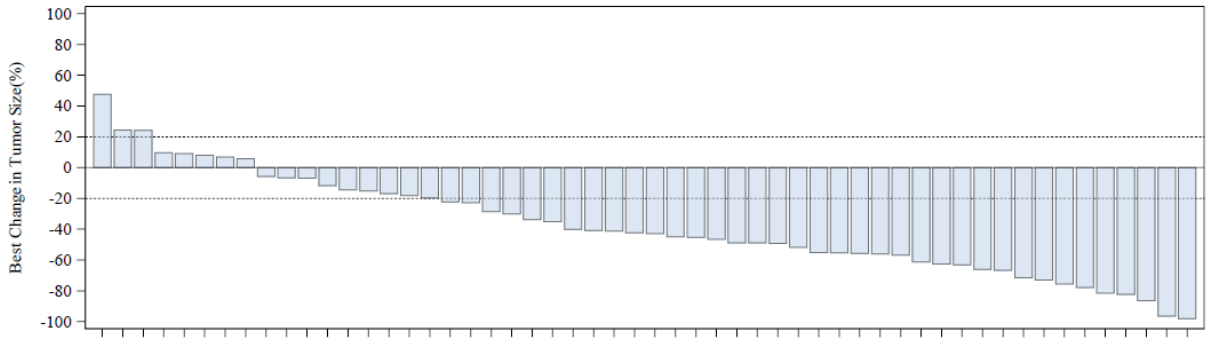
Percentages for event type were based on the total number of events and out of the number censored for the reasons for censoring.

Secondary endpoint : Change in tumour volume over time

Updated results:

As of 12 June 2024, the median best average percentage change from baseline in target plexiform neurofibroma (PN) tumour volume of was -42.62 in the paediatric cohort and -41.25% in the adult cohort.

Figure 19: Waterfall plot of best percent change from baseline in tumour volume – paediatric cohort (Study MEK-NF-201, FAS, data cut-off 12 June 2024)

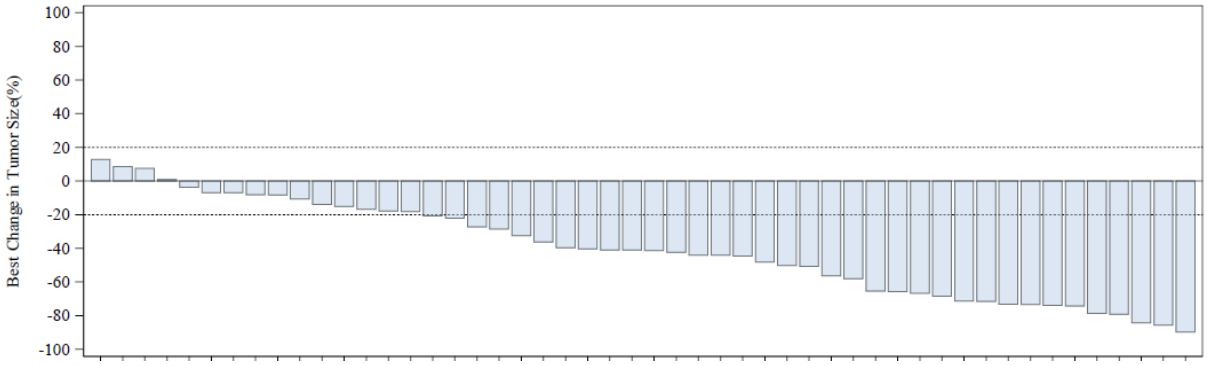


Abbreviations: FAS: Full Analysis Set; PN: plexiform neurofibroma.

Tumour volume measurements were taken for target PN tumours and independently calculated by 2 reviewers. The 2 calculated volumes were averaged to give the visit volume assessment, unless they represented different response statuses, in which case the reader assessment chosen by adjudication was used.

Tumour volume recorded at screening was considered as baseline.

Figure 20: Waterfall plot of best percent change from baseline in tumour volume – adult cohort (Study MEK-NF-201, FAS, data cut-off 12 June 2024)



Abbreviations: CSR: clinical study report; FAS: Full Analysis Set; PN: plexiform neurofibroma.
Tumour volume measurements were taken for target PN tumours and independently calculated by 2 reviewers.
The 2 calculated volumes were averaged to give the visit volume assessment, unless they represented different response statuses, in which case the reader assessment chosen by adjudication was used.
Tumour volume recorded at screening was considered as baseline.

Secondary Endpoints: PRO Assessments

Quality of life

A secondary endpoint was change from baseline in PedsQL at Cycle 13. Higher scores indicate better outcomes.

At Cycle 13, in the paediatric cohort the LS mean change from baseline at Cycle 13 in PedsQL total score 4.01 (95% CI: -0.74, 8.76; p = 0.096) by self-report and 5.64 (95% CI: 1.75, 9.53; p = 0.005).

At Cycle 13, in the adult cohort the LS mean change from baseline at Cycle 13 in PedsQL total score was 3.94 (95% CI: 0.70, 7.17; p = 0.018).

Numerical rating scale-11 NRS-11

Pain intensity was measured by the change from baseline in Numerical Rating Scale-11 (NRS-11) at Cycle 13. Lower scores indicate decreased pain.

At Cycle 13, in the paediatric cohort, 15 (41%) the LS mean change from baseline at Cycle 13 in NRS-11 was -0.79 (95% CI: 1.28, 0.29; p = 0.003).

At Cycle 13, in the adult cohort, the LS mean change from baseline at Cycle 13 in NRS-11 was -1.33 (95% CI: -1.83, -0.84; p < 0.001).

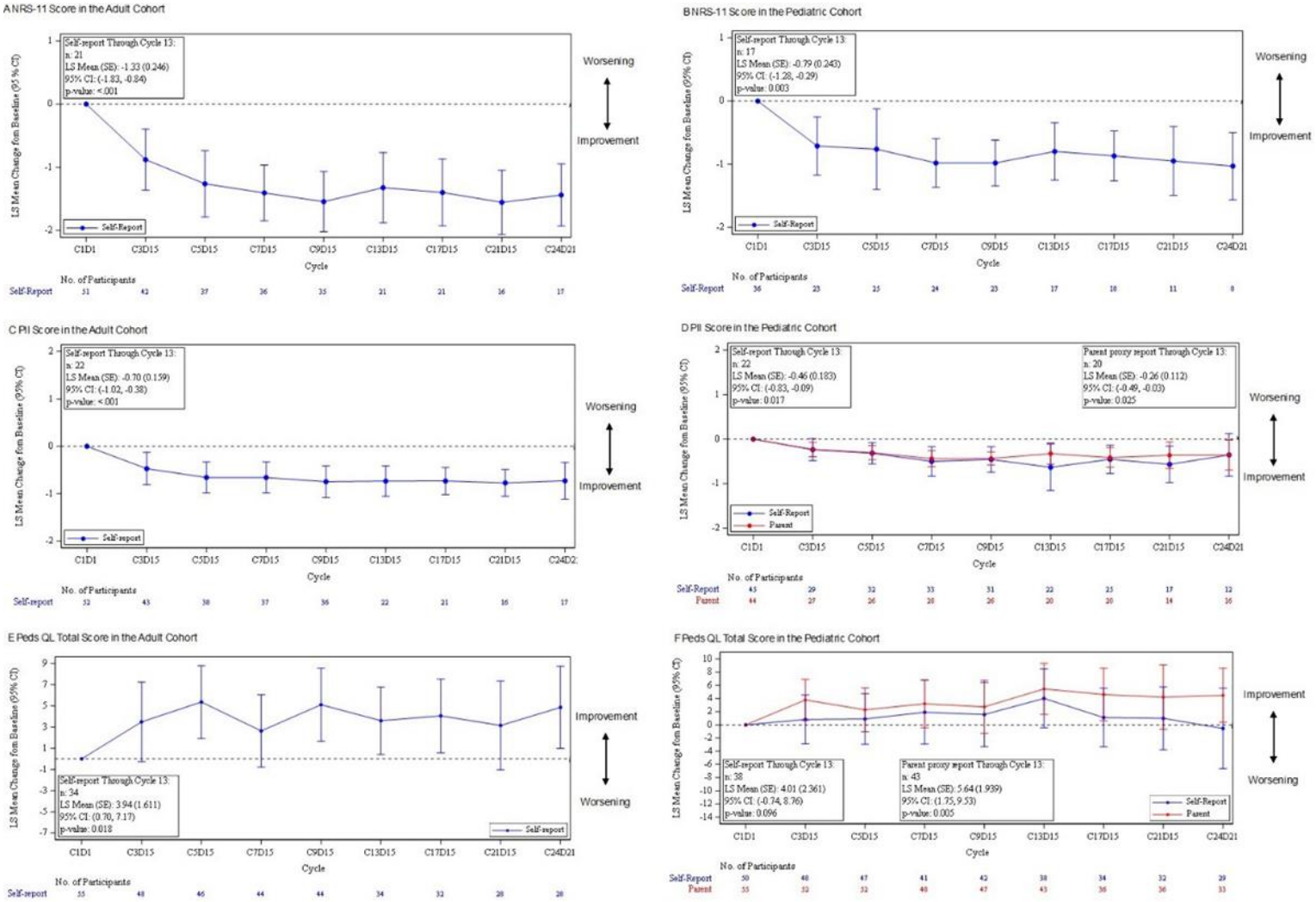
Pain Interference Index PII

Pain interference was measured by the change from baseline in the Pain Interference Index (PII) at Cycle 13. Lower scores indicate decreased pain interference with participants' daily activities.

At Cycle 13, in the paediatric cohort the LS mean change from baseline at Cycle 13 in PII was -0.46 (95% CI: -0.83, -0.09; p = 0.017) by paediatric self-report and -0.26 (95% CI: -0.49, -0.03; p = 0.025) by paediatric parent proxy.

At Cycle 13, in the adult cohort, the LS mean change from baseline at Cycle 13 in PII was -0.70 (95% CI: -1.02, -0.38; p < 0.001).

Figure 21: Mixed model repeat measures: change from baseline in PRO assessments



Abbreviations: C: cycle; D: day; NRS-11: Numeric Rating Scale-11; PedsQL: Paediatric Quality of Life Inventory; PII: Pain

Exploratory Endpoint: Time to Response

Time to response is defined as the time in months from the start of treatment to the date of first response that was subsequently confirmed.

Table 23: Time to response: full analysis set

	Paediatric (N = 56)	Adult (N = 58)
Time to Response (Months)		
n	29	24
Mean (StD)	8.63 (4.801)	9.71 (5.804)
Median	7.90	7.75

Min, Max	4.1, 18.8	4.0, 19.0
Cycle of Onset of Confirmed Response		
Cycle 5	13 (44.8%)	11 (45.8%)
Cycle 9	5 (17.2%)	2 (8.3%)
Cycle 13	6 (20.7%)	4 (16.7%)
Cycle 17	3 (10.3%)	3 (12.5%)
Cycle 21	2 (6.9%)	4 (16.7%)

Abbreviations: FAS: Full Analysis Set; Max: maximum; Min: minimum; StD: standard deviation.
Data Cut-Off 20 Sep 2023

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24: Summary of efficacy for trial MEK-NF-201 (ReNeu)

Title: A Phase 2b Trial of the MEK 1/2 Inhibitor (MEKi) PD-0325901 in Adult and Paediatric Patients with Neurofibromatosis Type 1 (NF1)-Associated Inoperable Plexiform Neurofibromas (PNs) that are Progressing or Causing Significant Morbidity			
Study identifier	MEK-NF-201		
Design	Ongoing open-label, multi-centre, phase IIb study being conducted to determine the efficacy and safety of mirdametinib in participants ≥ 2 years old with an inoperable NF1-associated PN causing significant morbidity. This study consists of two phases: the Treatment Phase and the optional Long-Term Follow-Up (LTFU) Phase; the LTFU Phase is currently ongoing.>		
	Duration of main phase: Duration of Extension phase:		24 cycles until a withdrawal criterion is met or mirdametinib is commercially available
Hypothesis	The null hypothesis for the adult population is that the objective response rate (ORR) is less than or equal to 23%. The alternative hypothesis is that the ORR is greater than 23%. The null hypothesis for the paediatric population is that the ORR is less than or equal to 20%. The alternative hypothesis is that the ORR is greater than 20%.		
Treatments groups	mirdametinib		2 mg/m2 BID, using an intermittent regimen (3 weeks on/1 week off) in 28-day cycles.
Endpoints and definitions	Primary endpoint	Objective response rate ORR	Percentage of patients with complete or partial response (PR) based on NCI POB central analysis using volumetric MRI analysis and per REiNS criteria, i.e. complete disappearance of target PN or decrease in volume of target PN by ≥20% compared with baseline
	Secondary	DoR	Duration of response
	Secondary	PedsQL	Quality of life at week 13

Title: A Phase 2b Trial of the MEK 1/2 Inhibitor (MEKi) PD-0325901 in Adult and Paediatric Patients with Neurofibromatosis Type 1 (NF1)-Associated Inoperable Plexiform Neurofibromas (PNs) that are Progressing or Causing Significant Morbidity			
Study identifier	MEK-NF-201		
	Secondary	PII	Pain Interference Index at week 13
	Secondary	NRS-11	Numerical Rating Scale-11 at week 13
Database lock	Study ongoing 20 Sep 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS Median follow-up (range): 24.0 cycles (0.0 to 36.0)		
Descriptive statistics and estimate variability	Treatment group	mirdametinib	
	Number of subjects	Paediatric 56	Adult 58
	ORR (%)	51.8	41.4
	95% confidence interval (CI)	38.0, 65.3	28.6, 55.1
	DoR median	not reached	not reached
	DoR≥12 months	26 (90%)	21 (88%)
	DoR≥24 months	14 (48%)	12 (50%)
	PedsQL LS mean change from baseline	4.01 self-reported 5.64 parent proxy	3.94
	95% confidence interval (CI)	-0.74, 8.76 1.75, 9.53	0.70, 7.17
	NRS-11 LS mean change from baseline	-0.79	-1.33
	95% confidence interval (CI)	1.28, 0.29	-1.83, -0.84
	PII LS mean change from baseline	-0.46 self-reported -0.26 parent proxy	-0.70
	95% confidence interval (CI)	-0.83, -0.09 -0.49, -0.03	-1.02, -0.38

2.6.5.4. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non Controlled Trials	2	0	0

2.6.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Comparisons to external control data

The single-arm study MEK-NF-201 has an exploratory objective to compare mirdametinib to historical controls. Two historical controls were included:

1. Placebo control arm of the National Cancer Institute (NCI) study 01-C-0222 (NCT00021541; A Phase II Randomized, Cross-Over, Double-Blinded, Placebo-Controlled Trial of the Farnesyltransferase Inhibitor R115777 in Paediatric Patients with NF1 and Progressive PNs)

2. NCI Study 08-C-0079 (NCT00924196; Natural History Study and Longitudinal Assessment of Children, Adolescents, and Adults with NF1).

Studies design

Study 01-C-0222

Study 01-C-0222 was an NCI-sponsored phase II randomized, double-blinded, placebo-controlled cross-over study of tipifarnib, in children and young adults (aged 3-25 years) with NF1 and progressive PNs at baseline with the potential to cause significant morbidity.

The primary endpoints were TTP, ORR, and the incidence of adverse events. PN volumes were measured with MRI at the start of Cycles 1, 4, 7, and 10, followed by every 6 cycles. Progression was defined as ≥20% volume increase in at least 1 target PN compared with baseline; a response was defined as ≥25% reduction in the sum of the volume of all index lesions for ≥4 weeks.

Study 08-C-0079

Study 08-C-0079 is an NCI-sponsored observational and longitudinal analysis of participants with clinically confirmed NF1 or a known NF1 mutation to characterize the natural history of NF1. New participants evaluated at the NIH were ≤35 years

Participants in the study were allowed to undergo clinically indicated surgeries and medical treatments and concurrently enrol in clinical trials for PNs. Participants remain on study until they met the criteria for discontinuation (including withdrawal of consent, serious protocol violation, lost to follow-up, or completed study objectives per the principal investigator).

The primary objective of the study is to longitudinally characterize and analyse NF1-related tumour and non-tumour manifestations. Endpoints included longitudinal volumetric analysis and growth rate assessment of target PNs, NF1-related pain and neuropathy, neuropsychological function, motor function, and quality of life, among others. MRIs of PNs were performed at baseline, every year until age 18 years, and then approximately every 3 years.

NCI provided data to the applicant for participants who enrolled in the study between 08 September 1999 and 15Oct2018. For adults aged ≥18 years, NCI provided MRIs and volumetric imaging of PN for treatment-naïve NF1 participants with at least 2 imaging scans available, or at least 2 imaging scans available prior to exposure to therapy, or at least 2 imaging scans available ≥6 months after therapy. For paediatric participants (<18 years old), NCI provided completed volumetric analysis for participants with NF1 PN.

Statistical methods

Exploratory objectives and endpoints

Table 25: Exploratory objectives and endpoints for comparisons to external control data

Exploratory Objectives	Exploratory Endpoints
Assess TTP and PFS of mirdametinib (Study MEK-NF-201) vs historical controls (Studies 01-C-0222 and 08-C-0079)	• TTP, defined as the elapsed time in months from treatment start date (Cycle 1 Day 1 [C1D1]) to the first date of progression (defined as target PN increase >20% compared to baseline) as measured by MRI. • PFS is defined as the time in months between either the start of treatment (when compared to Study 01-C-0222) or the date of baseline tumor assessment (when compared to Study 08-C-0079) and the earliest date of radiographic disease progression or death from any cause.
Assess rate of change in target PN volume over time in participants treated with mirdametinib vs historical controls (Studies 01-C-0222 and 08-C-0079)	Yearly percentage change from baseline in target PN volume

Abbreviations: PFS: progression-free survival; PN: plexiform neurofibroma; TTP: time to progression.

Analysis sets

The 3 exploratory endpoints from participants from the FAS in study MEK-NF-201 were compared to those in studies 01-C-0222 and 08-C-0079.

Three historical controls were used to assess the effect of mirdametinib.

These analyses also include appropriate adjustment for potential imbalances in important baseline participant characteristics across the studies due to different populations. Two balancing procedures, one-to-one propensity score matching and inverse probability of treatment weighting (IPTW), were performed to balance important baseline prognostic factors between participants from study MEK-NF-201 and historical controls to reduce potential bias and is described below.

Data were missing for height, weight, and body surface area (BSA), so these factors were not available for cohort matching.

For each endpoint, 3 sets of results were generated for comparisons versus historical control:

- All participants
- Participants selected using one-to-one propensity score matching.
- Comparisons using inverse probability of treatment weighting.

Table 26: Cohorts to be used in comparisons to external control

	Treatment Group	
Cohort (a)	**Active Arm in MEK-NF-201**	**Historical Control**
1	Paediatric participants with progressive PN (age 2 to <18 years)	Placebo arm in the Study 01-C-0222 (age <18 years)
2	Paediatric participants (age 2 to <18 years)	Paediatric cohort in Study 08-C-0079 (age 2 to <18 years)
3	Adult participants (age 18 years or older)	Adult cohort in Study 08-C-0079 (age 18 years or older)

Abbreviations: PN: plexiform neurofibroma.
Note: Age was the age at the time of enrolment for Studies MEK-NF-201 and 01-C-0222 and the age of baseline MRI scans for Study 08-C-0079.

Planned analyses

All planned analyses for comparisons to external control were exploratory. For each endpoint, treatment comparison was to be performed in each of the 3 above cohorts.

Disposition, demographics, and baseline characteristics were summarized if available from studies 01-C-0222 and 08-C-0079. To account for potential differences in baseline characteristics due to differences in participant populations enrolled in the 3 studies, both propensity score matching and IPTW were conducted as described below.

For studies MEK-NF-201 and 01-C-0222, baseline was defined as the last assessment before the first administration of study treatment. For study 08-C-0079, baseline was defined as the first assessment on or after enrolment.

Missing values were not imputed. Participants must have at least one non-missing value for the endpoints of interest to be included in the matching procedure.

For yearly percentage change from baseline in target PN volume, participants with a non-missing value were those with baseline and at least one post-baseline tumour assessment within the windows defined in Natural History SAP. For TTP, participants must have had baseline and at least one post-baseline tumour assessment to have been considered having a non-missing value. This rule also applied to PFS, unless death occurred before any post baseline tumour assessment.

Propensity Score Balancing Methods

Comparisons between participants from study MEK-201 and the historical control studies, studies 01-C-0222 and 08-C-0079 without appropriate adjustment (i.e. selecting participants with similar baseline characteristics) may generate biased results since participants were not randomly assigned to the treated and control groups, and there could be systematic differences between these 2 groups of participants. The objective of matching was to balance the baseline prognostic factors between participants in MEK-NF-201 and historical controls while minimizing the loss of information and sample size.

The following 3 baseline characteristics were considered important prognostic factors for disease progression and were included in the model for propensity score matching if the information was available from the study:

a) Age

b) Lesion type: (Distinct nodular lesion or solitary nodular) vs. other.

c) Prior MEK inhibitor treatment: (Y/N).

For study 01-C-0222 (paediatric participants with NF1 and progressive PN at baseline treated with placebo), age was the only baseline characteristic used in balancing methods since the data received do not contain prognostic factors b) or c). For study 08-C-0079, the data includes all 3 prognostic factors.

To account for potential differences in baseline characteristics between participants from study MEK-NF-201 and the historical control studies, the following balancing methods were conducted with the above 3 baseline prognostic factors, as applicable to the study:

1. One-to-one propensity score matching without replacement

2. Inverse probability of treatment weighting (IPTW).

Analysis of Yearly Percentage Change from Baseline in Target PN Volume

For each cohort, an analysis of covariance (ANCOVA) model was applied for treatment comparison between participants from study MEK-NF-201 and the historical control.

Comparisons of this endpoint were made at each year up to 3 years. Since the 2 studies for historical controls may not have the same assessment time points as study MEK-NF-201, a window of ± 6 months was used for the comparison time points at months 12, 24, 36, etc. Comparisons were performed if each treatment group had at least 5 participants for yearly percentage change from baseline in target PN volume after propensity score matching. In the model, the yearly percentage change from baseline in target PN volume was the dependent variable, and age and target PN volume at baseline were the covariates.

For each comparison, the percentage change in tumour volume per year was summarized.

The estimated percentage change in tumour volume in each treatment and their difference with associated 95% CI through ANCOVA was displayed.

Analysis of Time to Progression (TTP)

TTP for each cohort was analysed using the Kaplan-Meier method, with quartiles and associated 95% CI calculated using the log-log transformation, if estimable. Survival curves for both treatment groups in the same cohort were presented. Within each cohort, the p-value for treatment comparison was calculated using a log rank test; the hazard ratio and its 95% CI for study MEK-NF-201 versus studies 01-C-0222 and 08-C-0079 were estimated with a Cox regression model using treatment group, age, and target PN volume at baseline as covariates.

Participants not experiencing radiographic disease progression were censored on the last adequate MRI assessment that verified lack of disease progression.

Analysis of Progression Free Survival (PFS)

PFS was analysed using the Kaplan-Meier method, with quartiles and associated 95% CI calculated using the log-log transformation, if estimable. Survival curves for both treatment groups in the same cohort were presented. Within each cohort, the p-value for treatment comparison was calculated using a log rank test; the hazard ratio and its 95% CI for the study MEK-NF-201 versus studies 01-C-0222 and 08-C-0079 were estimated with a Cox regression model using treatment group, age, and target PN volume at baseline as covariates. Participants not experiencing radiographic disease progression or death were censored on the last adequate MRI assessment that verified lack of disease progression or death.

Demographic and other baseline characteristics

A summary of the demographic characteristics for each of the three cohorts is presented in Table 27.

Table 27: Demographics and other baseline characteristics

	Cohort 1		Cohort 2		Cohort 3	
	Study MEK-NF-201 paediatric Participants with Progressive PN (N=34)	Study 01-C-0222 Paediatric Participants with Progressive PN (N=29)	Study MEK-NF-201 Paediatric Participants (N=54)	Study 08-C-0079 paediatric Participants (N=77)	Study MEK-NF-201 Adult Participants (N=50)	Study 08-C-0079 Adult Participants (N=44)
Age (Years)[1]						
N	34	29	54	77	50	44
Mean (StD)	9.6 (4.63)	8.9 (4.38)	9.9 (4.48)	9.7 (4.49)	35.3 (13.16)	22.9 (6.81)
Median	10.0	8.0	10.0	10.0	35.0	19.0
Min, Max	2, 17	3, 17	2, 17	0, 17	18, 69	18, 45
Gender						
Male	15 (44.1%)	14 (48.3%)	25 (46.3%)	43 (55.8%)	18 (36.0%)	24 (54.5%)
Female	19 (55.9%)	15 (51.7%)	29 (53.7%)	34 (44.2%)	32 (64.0%)	20 (45.5%)
Race						
White	23 (67.6%)	25 (86.2%)	37 (68.5%)	55 (71.4%)	42 (84.0%)	35 (79.5%)
Non-White	11 (32.4%)	4 (13.8%)	17 (31.5%)	21 (27.3%)	8 (16.0%)	7 (15.9%)
Unknown	0	0	0	1 (1.3%)	0	2 (4.5%)
Ethnicity						
Hispanic Or Latino	6 (17.6%)	1 (3.4%)	8 (14.8%)	5 (6.5%)	1 (2.0%)	4 (9.1%)
Not Hispanic Or Latino	26 (76.5%)	28 (96.6%)	43 (79.6%)	0	46 (92.0%)	37 (84.1%)
Missing/Not Reported/ Unknown	2 (5.9%)	0	3 (5.6%)	72 (93.5%)	3 (6.0%)	3 (6.8%)
Tumour Location[2]						
Head and/or Neck and/or Chest	19 (55.9%)	0	28 (51.9%)	29 (37.7%)	24 (48.0%)	17 (38.6%)
Other	15 (44.1%)	0	26 (48.1%)	48 (62.3%)	26 (52.0%)	27 (61.4%)
Missing	0	29 (100%)	0	0	0	0
Prior MEK Inhibitor Treatment (yes/no)						
Yes	4 (11.8%)	0	6 (11.1%)	0	4 (8.0%)	8 (18.2%)
No	30 (88.2%)	0	48 (88.9%)	77 (100%)	46 (92.0%)	36 (81.8%)
Missing	0	29 (100%)	0	0	0	0
Lesion Type[4]						
Solitary Nodular	2 (5.9%)	0	2 (3.7%)	10 (13.0%)	4 (8.0%)	20 (45.5%)
Typical Nodular	32 (94.1%)	0	52 (96.3%)	67 (87.0%)	46 (92.0%)	24 (54.5%)
Missing	0	29 (100%)	0	0	0	0

Abbreviations: BSA: body surface area; N/A: not applicable.
Paediatric participants: age <18 years; Adult participants: age ≥18 years. 0 age means the participant age could be less than 1 year. Participants who do not have any post baseline MRI are excluded.
1 Age was defined as the age at enrolment for MEK-NF-201 and 01-C-0222. For 08-C-0079, age was the age at baseline MRI scans.
2 Similar to Study MEK-NF-201, tumour locations were categorized as follows:

• Head and/or Neck and/or Chest including: Head and neck/Head/neck/head neck chest/neck chest. Other, including: Mesentery and pelvis/Trunk/trunk and extremity/abdominal wall/chest wall/extremity.
3 BSA(m2) was calculated according to the Du Bois formula as: BSA(m2) = 0.007184*Weight(kg)^0.425*Height(cm)^0.725.
4 Collected as distinct nodular/not a distinct nodular lesion in NCI studies and nodular/solitary nodular/typical in Study MEK-NF-201, categorized as typical nodular vs solitary nodular.

Efficacy evaluation

Yearly Percentage Change in Target PN

Cohort 1

At Year 1, Year 2, Year 3, and the last assessment, paediatric participants with progressive PN at baseline from study MEK-NF-201 had a decrease in yearly percentage change in target PN volume as compared to an increase in yearly percentage change in the target PN volume in participants from study 01-C-0222.

Cohort 2

At Year 1, Year 2, Year 3, and the last assessment, paediatric participants from study MEK-NF-201 had a decrease in yearly percentage change in target PN volume as compared to an increase in yearly percentage change in the target PN volume in participants from study 08-C-0079.

Cohort 3

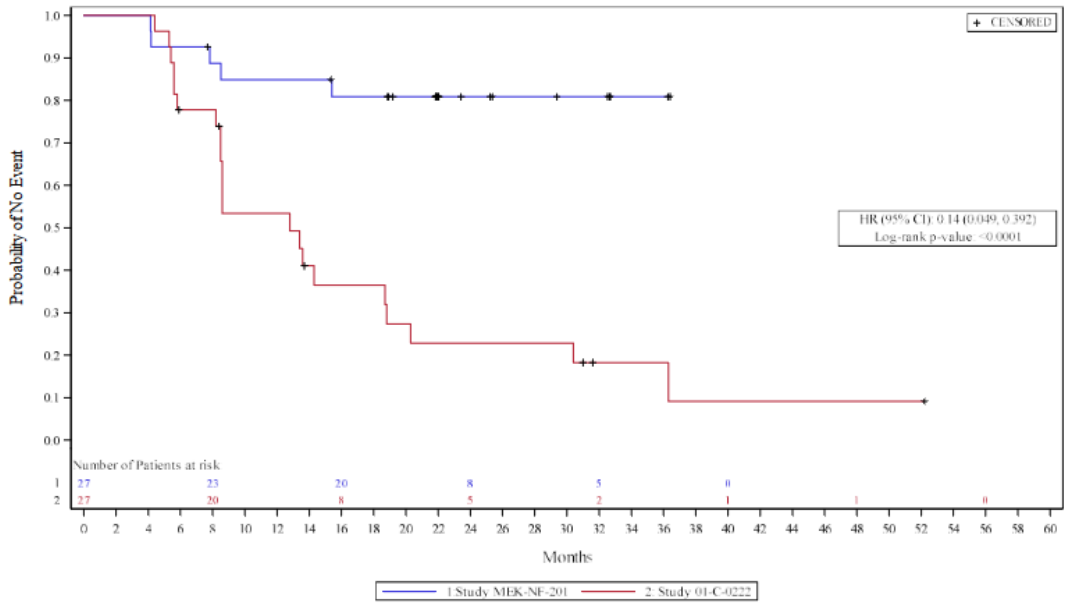
At Year 1, Year 2, Year 3, and the last assessment, participants from study MEK-NF-201 had a substantial decrease in yearly percentage change in target PN volume as compared to an increase in yearly percentage change in the target PN volume in participants from study 08-C-0079.

Time to Progression (TTP)

Cohort 1

The median TTP (95% CI) was not reached for participants from Study MEK-NF-201 by all analyses (before matching, after propensity score matching, or after IPTW). In study 08-C-0079 the median the medians TTP (95% CI) in months were 19.71 (16.13, 24.15) before matching, 21.75 (16.36, 32.30) after propensity score matching, and 20.63 (16.36, 30.62) after IPT.

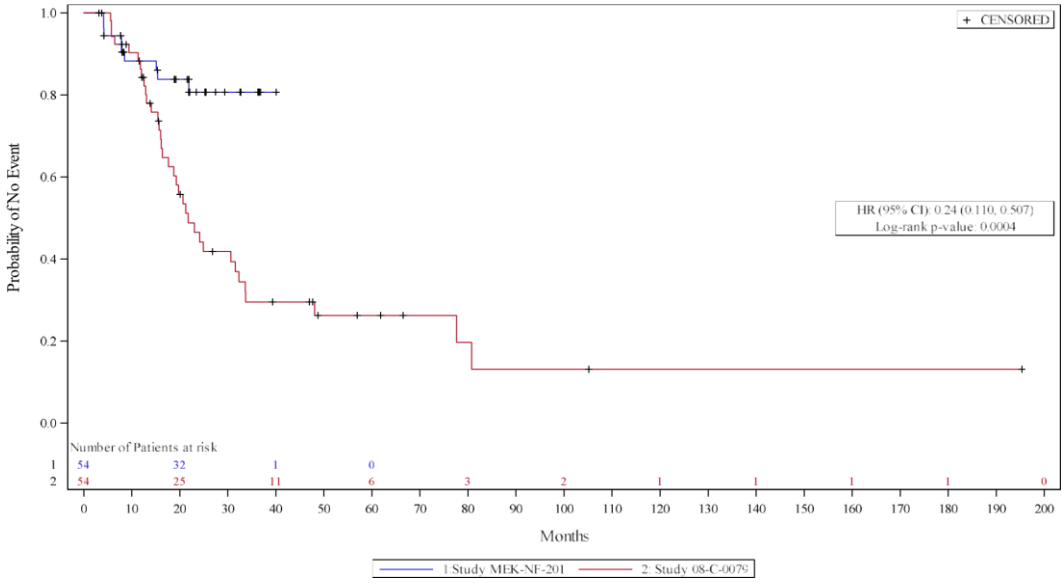
Figure 22: Kaplan-Meier plot of time to progression after propensity score matching – cohort 1



Cohort 2

A total of 9 (17%) participants from Study MEK-NF-201 had disease progression and there were no deaths. A total of 55 (71%) participants from Study 08-C-0079 had an event (progression or death) both before matching and after IPTW; 54 (98%) participants progressed, and 1 (2%) participant died. A total of 36 (67%) participants from Study 08-C-0079 had an event (progression or death) after propensity score matching; 35 (97%) progressed and 1 (3%) died.

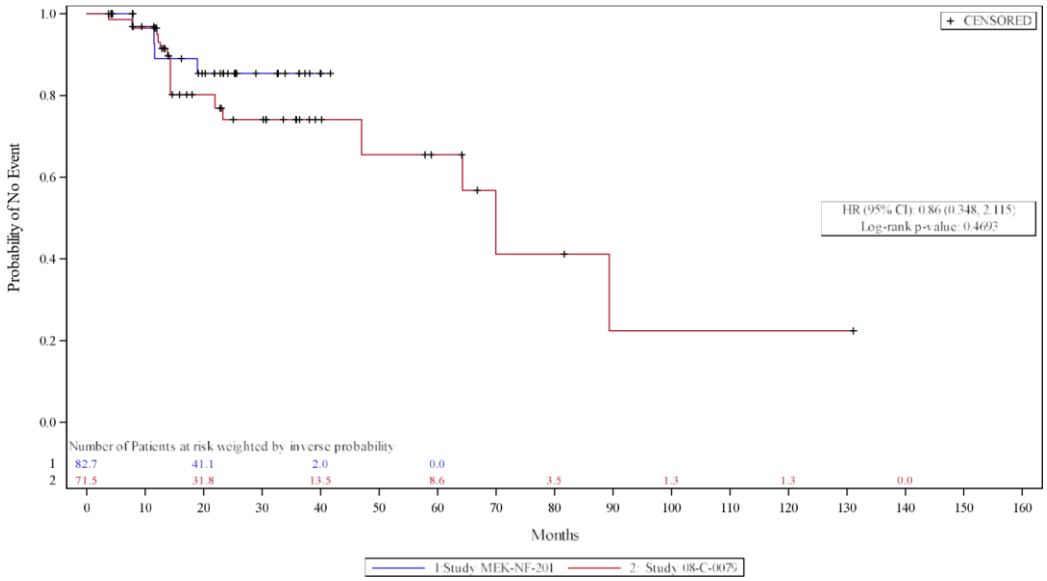
Figure 23: Kaplan-Meier plot of time to progression after propensity score matching – cohort 2



Cohort 3

The median TTP (95% CI) was not reached for participants from Study MEK-NF-201 by all analyses (before matching, after propensity score matching, or after IPTW, respectively). In contrast, there were substantially more events in participants from Study 08-C-0079 and the median was reached; the median TTP (95% CI) in months was 69.98 before matching, after propensity score matching, and after IPTW with different 95% CIs for each, (47.02, NE), (14.32, NE), and (47.02, NE), respectively.

Figure 24: Kaplan-Meier plot of time to progression after IPTW – cohort 3



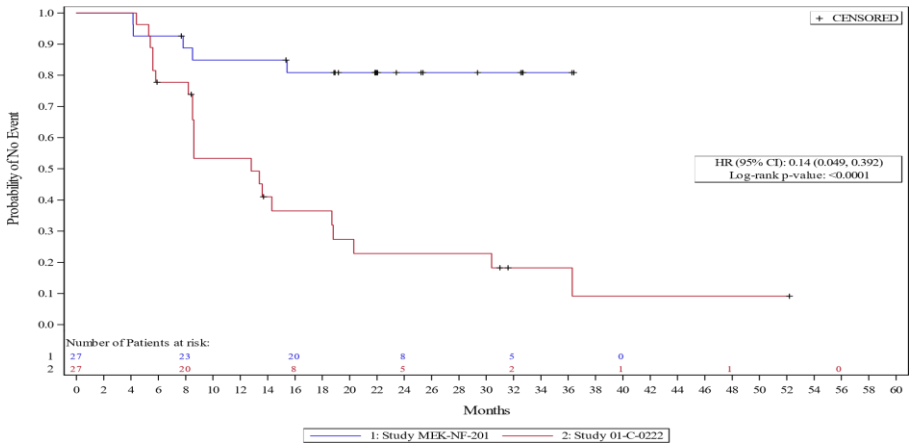
Participant MEK-NF-201-038-001 was excluded from IPTW after the first round of IPTW due to weight = 75.05.

Progression-Free Survival (PFS)

Cohort 1

There were no deaths reported among paediatric participants with progressive PN at baseline from participants Study MEK-NF-201 or those in Study 01-C-0222. As a result, the results from the PFS and sensitivity analyses were the same as the corresponding analyses for TTP.

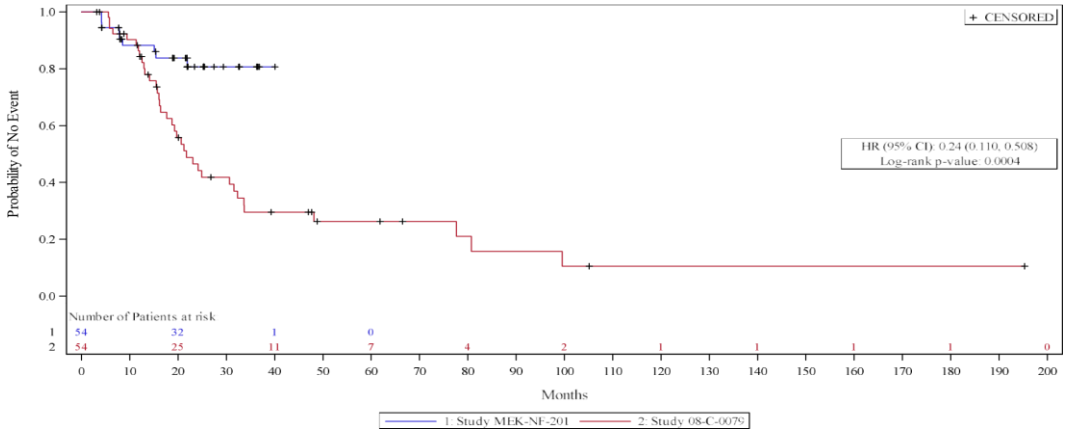
Figure 25: Kaplan-Meier Plot of progression-free survival after propensity score matching – cohort 1



Cohort 2

The median PFS (95% CI) was not reached for participants from Study MEK-NF-201. In the historical control the median PFS (95% CI) in months were 19.71 (16.13, 24.15) before matching, 21.75 (16.36, 32.30) after propensity score matching, and 20.63 (16.36, 30.62) after IPTW.

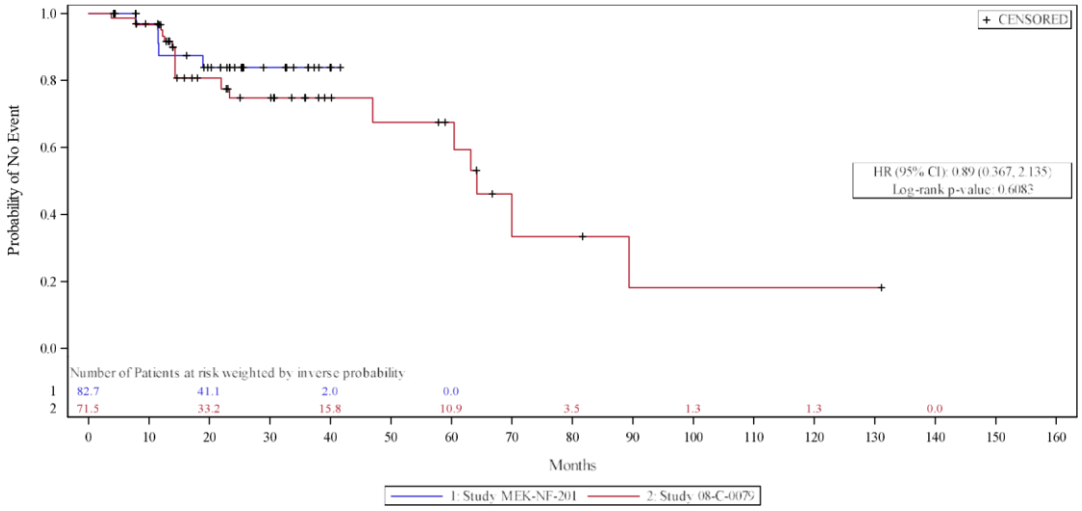
Figure 26: Kaplan-Meier plot of progression-free survival after propensity score matching – cohort 2



Cohort 3

The median PFS (95% CI) was not reached for participants from Study MEK-NF. In study 08-C-0079 and the median was reached; the medians PFS (95% CI) in months were 64.23 (47.01, 89.36) before matching, 60.47 (47.01, NE) after propensity score matching, and 64.23 (47.01, 89.36) after IPTW.

Figure 27: Kaplan-Meier Plot of progression-free survival after IPTW – cohort 3



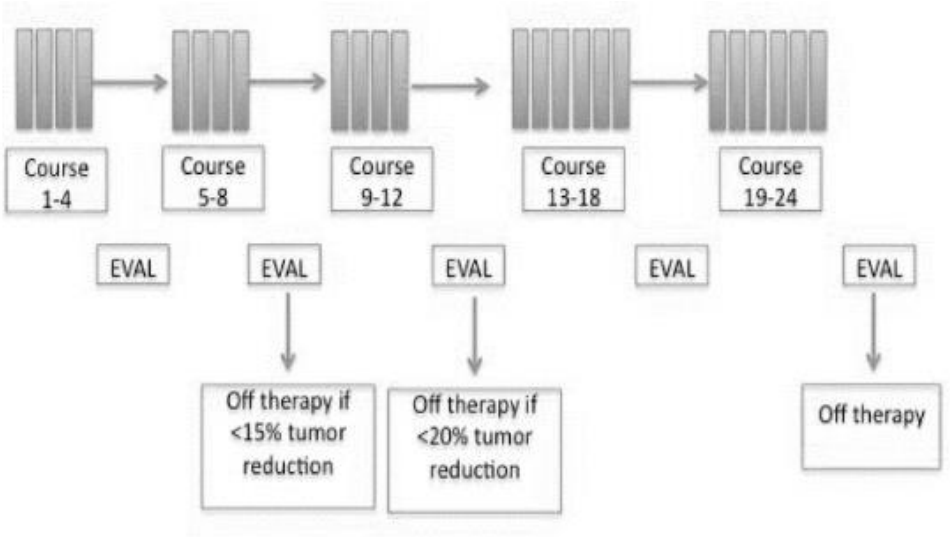
2.6.5.7. Supportive study

Study NF 106

NF-106 was an open-label, multi-centre, phase II study that aimed to evaluate adolescents and adults (≥16 years of age) with neurofibromatosis type 1 (NF1) and morbid or progressing plexiform neurofibromas (PNs).

Participants received 8 cycles of treatment. Continuation of study treatment was permitted beyond Cycle 8 if participants had achieved at least a 15%volumetric reduction from baseline. Additionally, continuation of study treatment beyond Cycle 12 was permitted if at least a 20% volumetric reduction was achieved. If either of these benchmarks were not met, the participant was discontinued from treatment.

Figure 28: Study design



The study population comprised male and female participants aged ≥ 16y with either the clinical diagnosis of NF1 using the NIH Consensus Conference criteria of at least 1 other diagnostic criterion or have a constitutional NF1 mutation. Participants had to have one or more NPs that were progressive OR causing significant morbidity. Participants had to have measurable PN(s) amenable to volumetric MRI analysis. Participants previously treated with a MEK inhibitor were excluded.

The study treatment consisted of mirdametinib 1 mg capsules. Participants received mirdametinib at a dose of 2 mg/m^2 /dose BID with a maximum dose of 4 mg BID.

Table 28: Objectives / endpoints for study NF 106

Objectives	Endpoints
Primary	
To evaluate the confirmed objective response rate ORR (CR + PR) of mirdametinib using volumetric MRI analysis, in participants with NF1 and PNs.	Confirmed ORR defined as the proportion of participants who have a BOR of PR or CR by the end of treatment with ≥4 weeks duration.
Secondary	
To evaluate the safety and tolerability of Objectives Endpoints mirdametinib in participants with NF1 and symptomatic inoperable PN as measured by the incidence of AEs and changes from baseline in laboratory parameters and vital signs.	Safety endpoints included incidence of TEAEs, SAEs, AESIs, changes from baseline in laboratory parameters and vital signs, and retinal exam abnormalities.

Objectives	Endpoints
To evaluate durability of response as measured by DoR.	DoR for participants whose best response was CR or PR.
To evaluate the effect of mirdametinib on pain and QoL as measured by the NRS-11, the BPI, and the PedsQL NF1 module.	Change in pain and QoL scores from baseline as measured by the NRS-11, BPI, and PedsQL NF1 module.
To characterize the pharmacokinetic profile of mirdametinib (and the metabolite PD-0315209) when administered to this participant population.	The following PK parameters calculated using a non-compartmental method: Cmax, Tmax, AUClast, AUC0-8h, Tlast.

Abbreviations: AE: Adverse events; BPI: Brief pain inventory; CR: Complete response; DoR: Duration of response; ORR: Objective response rate; MRI: Magnetic resonance imaging; PedsQL: Paediatric quality of life inventory; PR: Partial response; NF-1: Neurofibromatosis type 1; NRS-11: Numeric rating scale-11; PN: Plexiform neurofibroma QoL: Quality of life; TEAE: Treatment-emergent adverse event

The REiNS criteria for response were used to assess the primary endpoint for this study.

The target PNs were centrally evaluated by MRI by a single reader at the NCI Paediatric Oncology Branch.

Statistical methods

The planned sample size for the study was between 9 and 19 evaluable participants, with a target of 17 evaluable participants. To allow for 10% unevaluable participants, a maximum of 19 participants were planned to be enrolled. This sample size was based on three factors: safety based on risk versus benefit; efficacy of 25% ORR; and power of 80% to achieve feasibility if this rate was true.

The Full Analysis Set (FAS) was defined as all participants who received at least one dose. All demographic and baseline characteristics summaries, as well as efficacy and PRO analyses were conducted using this analysis population.

The Safety Analysis Set was defined as all participants and who took at least one dose of study treatment. The Safety Analysis Set was used for all safety analyses.

Results

Baseline data

There was a total of 19 participants in the FAS and the Safety Analysis Set, and 18 participants in the Pharmacokinetic Analysis Population.

Table 29: Summary of demography and baseline characteristics (FAS)

	Paediatric (N = 2)	Adult (N = 17)	Total (N = 19)
Age at informed consent date (years)			
n	2	17	19
Mean (StD)	16.0 (0)	25.9 (5.83)	24.8 (6.32)
Median	16.0	24.0	24.0
Minimum, Maximum	16, 16	18, 39	16, 39
Sex			
Male	1 (50.0%)	6 (35.3%)	7 (36.8%)
Female	1 (50.0%)	11 (64.7%)	12 (63.2%)

	Paediatric (N = 2)	Adult (N = 17)	Total (N = 19)
Race			
White	1 (50.0%)	7 (41.2%)	8 (42.1%)
Black or African-American	0	5 (29.4%)	5 (26.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	0	3 (17.6%)	3 (15.8%)
American Indian or Alaska Native	0	0	0
Other	0	2 (11.8%)	2 (10.5%)
Unknown or not reported	0	0	0
Multiple	1 (50.0%)	0	1 (5.3%)
Ethnicity			
Hispanic or Latino	0	2 (11.8%)	2 (10.5%)
Non-Hispanic	2 (100%)	14 (82.4%)	16 (84.2%)
Unknown or not reported	0	1 (5.9%)	1 (5.3%)

Abbreviations: FAS: Full analysis set; StD: Standard deviation.
Percentages were calculated using the FAS participants in the corresponding cohort as the denominator

Baseline Disease Characteristics

Table 30: Summary of baseline disease characteristics (FAS)

	Paediatric (N = 2)	**Adult (N = 17)**	**Total (N = 19)**
Target PN Location			
Mesentery & pelvis	1 (50.0%)	3 (17.6%)	4 (21.1%)
Head & neck	0	5 (29.4%)	5 (26.3%)
Paraspinal	0	3 (17.6%)	3 (15.8%)
Lower extremities	1 (50.0%)	1 (5.9%)	2 (10.5%)
Upper extremities	0	1 (5.9%)	1 (5.3%)
Abdominal wall	0	2 (11.8%)	2 (10.5%)
Chest wall	0	2 (11.8%)	2 (10.5%)
Baseline Target Tumour Volume (mL)			
n	2	17	19
Mean (StD)	2877.0 (3230.06)	553.2 (806.24)	797.8 (1301.64)
Median	2877.0	387.0	390.4
Minimum, Maximum	593.0, 5161.0	3.9, 3292.0	3.9, 5161.0

	Paediatric (N = 2)	Adult (N = 17)	Total (N = 19)
Any Non-target PNs?			
Yes	0	3 (17.6%)	3 (15.8%)
No	2 (100.0%)	14 (82.4%)	16 (84.2%)

Abbreviations: FAS: Full analysis set; PN: Plexiform neurofibroma; StD: Standard deviation.
Percentages were calculated using the FAS participants in the corresponding cohort as the denominator. Target PN location was derived from the key word (in parenthesis) associated with each category: mesentery & pelvis (pelvis), head & neck (neck/orbit) paraspinal (paraspinal), lower extremities (leg/foot/thigh w/o pelvis), upper extremities (arm/shoulder), abdominal wall (lumbosacral plexus), chest wall (brachila/brachial plexus).

Outcomes

Primary Endpoint: ORR

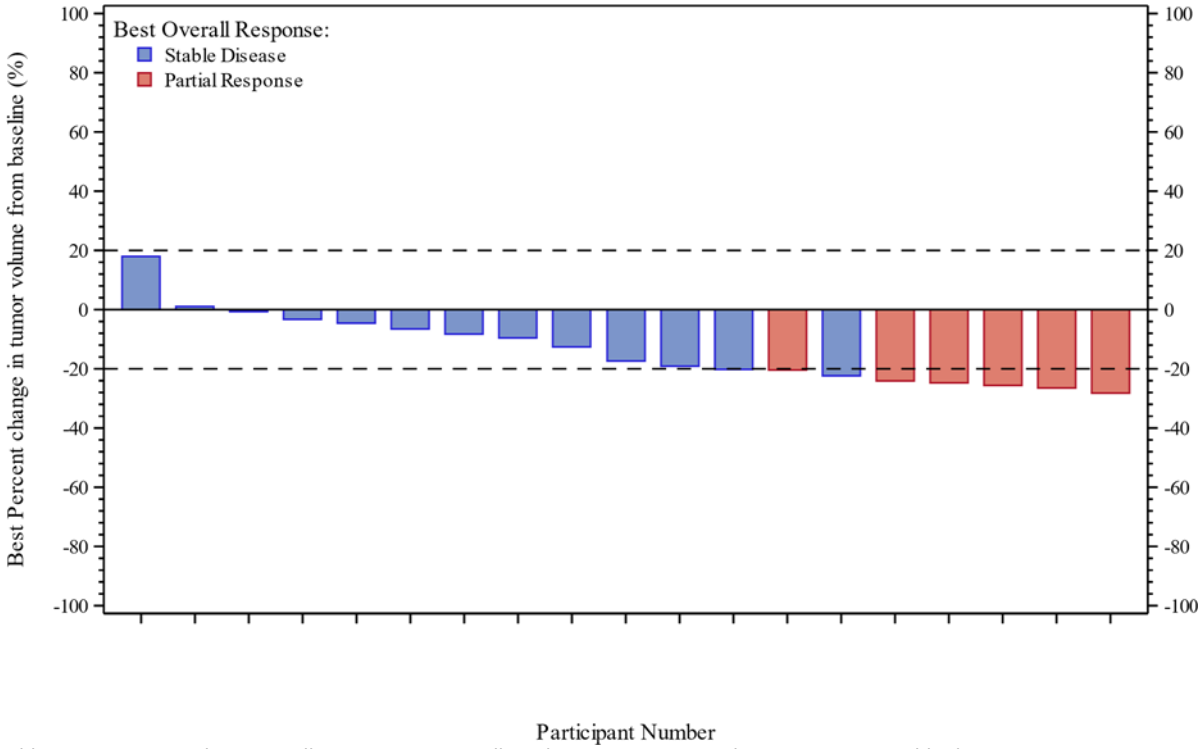
Table 31: Analysis of confirmed ORR (FAS)

	Paediatric (N (N = 2)	Adult (N = 17)	Total (N = 19)
Confirmed Objective Response			
n	1	5	6
ORR (%)	50.0	29.4	31.6
95% CI	(1.26, 98.74)	(10.31, 55.96)	(12.58, 56.55)
p-value	0.004	<0.001	<0.001
Best Overall Confirmed Response, n (%)			
Complete Response	0	0	0
Partial Response	1 (50.0%)	5 (29.4%)	6 (31.6%)
Stable Disease	1 (50.0%)	12 (70.6%)	13 (68.4%)
Progressive Disease	0	0	0
Not Evaluable	0	0	0

Abbreviations: BOR: Best overall confirmed response; CI: Confidence interval; CR: Complete response; FAS: Full analysis set; ORR: Objective response rate; PD: Progressive disease PR: Partial response; SD: Stable disease
Percentages were calculated using the FAS participants in the corresponding cohort as the denominator.
The levels of BOR are defined as follows: CR: A complete resolution of the target PN for ≥4weeks; PR: A ≥ 20% reduction in the volume of the target PN lesion compared to the pretreatment volume for ≥4 weeks; SD: Between a <20% increase and <20% decrease in the volume of the target PN lesion compared to the pretreatment volume for ≥4 weeks; PD: A ≥20% increase in the volume of the target PN compared to the pretreatment volume; Not evaluable: the volume could not be determined.
Confirmed ORR was defined as the proportion of participants who had a BOR of PR or CR by the end of treatment that lasted for ≥4 weeks. n is the number of confirmed objective responders in each column.
Exact two-sided 95% CIs were estimated using the Clopper-Pearson method. p-values were based on the two-sided binomial test evaluating the null hypothesis that the ORR is 5%.

The median (min, max) best percentage change from baseline in tumour volume was -17.14% (-28.0, 17.9)

Figure 29: Waterfall plot of best percentage change from baseline in tumour volume: FAS



Abbreviations: BOR: best overall response; FAS: Full Analysis Set; PR: partial response; SD: stable disease.
Note: One participant had a single PR that was not confirmed in a subsequent scan; therefore, their BOR is SD.

Secondary Endpoints - Duration of Response

Of the 6 (32%) confirmed responders, the median (95% CI) DoR was not estimable because all 6 responders were censored due to no PD/death post-confirmed response. Of these 6 responders, 5 participants maintained their response for at least 8 months.

Secondary Endpoints – NRS 11

Pain intensity was measured by the Numerical Rating Scale-11 (NRS-11); lower scores indicate decreased pain severity.

Of 19 participants, 9 completed the NRS-11 at Cycle 12 and 4 participants completed the NRS-11 at Cycle 24. There was an improvement in the least squared (LS) mean NRS-11 scores change from baseline at Cycle 12 (LS mean = -1.81, 95% CI: -3.44, -0.19; p= 0.030). At Cycle 24, the LS mean was -0.30 (95% CI: -2.14, 1.54; p=0.740) indicating decreased pain severity.

Secondary Endpoints – BPI

The Brief Pain Inventory (*BPI*) assesses the severity of pain and its impact on functioning; lower scores indicate decreased pain interference.

At Cycle 12, 9 participants completed the BPI. The median (min, max) change from baseline total score was -0.86 (-4.57, 0.86), indicating decreased pain interference. For the responder group (n=6), the median change from baseline (min, max) BPI total score at Cycle 12 was -0.29 (-4.57, 0.57).

Secondary Endpoints – PedsQL NF1 Module

Quality of life was assessed using the PedsQL NF1 Module; positive change from baseline indicates improvement

At Cycle 12, 9 participants completed the PedsQL NF1 module. The median (min, max) change from baseline at Cycle 12 was 3.6 (-20, 29), for the responder group, the total median (min, max) PedsQL NF1 module score at Cycle 12 was 2.0 (-20, 29) indicating an improvement in QoL.

2.6.5.8. Patient engagement

The following information was received in the context of a CHMP early dialogue with patient organisations:

NF Patients United (NFPU)

NF is one of the most common rare genetic conditions. However, access to treatment is inconsistent across the region. The only approved treatment for inoperable plexiform neurofibromas (PNs) is selumetinib (Koselugo), but it is primarily available for paediatric patients, creating significant challenges for adult patients. The patient community advocates for standardized access to treatments across all regions to ensure better choices and availability for all patients.

Additionally, transitioning from paediatric to adult care is difficult, often leading to patients disengaging from follow-ups and healthcare. This withdrawal from the healthcare system results in increased burdens on the patient's health and rising societal costs. Psychosocial issues are also widespread, with many NF1 patients suffering from anxiety, depression, isolation, and bullying. The lack of mental health support exacerbates these problems, and a notable percentage of NF patients report suicidal ideation.

For pregnant patients, managing NF1 becomes more complicated, as tumour growth can worsen during pregnancy, and treatment options are limited. There is a critical need for more research and support to help guide prenatal and postnatal care. Meanwhile, the current treatment's method of administration (as a pill) poses challenges, particularly for children who struggle with swallowing, while fasting requirements and medication-related restrictions vary between countries. The side effects of treatment, such as pain and impacts on multiple organs, also remain a significant concern for many patients, leading to demands for clearer guidelines on managing adverse effects.

The NF community also stresses the importance of personalized healthcare. Each patient's needs can differ based on factors such as age, gender, and socio-economic background, making patient and family involvement essential in treatment decisions. Even with side effects, having treatment options can vastly improve patients' mental health and overall quality of life. The surgical removal of PNs, which often leads to scarring and the regrowth of tumours, is usually less desirable than medication. A new drug that balances efficacy with fewer side effects could play a pivotal role in managing PNs sustainably.

Ultimately, each new treatment that shows positive safety and efficacy outcomes represents a significant improvement for NF patients, reducing the burden on healthcare systems and enhancing patients inclusion in society.

2.6.5.9. Healthcare provider engagement

The following information was received in the context of a CHMP early dialogue with healthcare professionals organisation (European Academy of Neurology):

The surgical management of plexiform neurofibromas (PNs) remains a challenging option, particularly because of the difficulty in fully removing the tumours and the high recurrence rate. In parallel, the development of MEK inhibitors like selumetinib, currently approved for paediatric patients with symptomatic and inoperable PNs, represents a significant breakthrough. However, there is ongoing research into other MEK inhibitors, including mirdametinib, trametinib, and binimetinib, aiming to

improve outcomes across broader patient groups, especially adults and patients who may not benefit from selumetinib due to side effects, or other contraindications, such as cardiac failure.

For optimal outcomes with these therapies, treatment duration and cycles are structured, often lasting up to one year, with personalized multidisciplinary follow-up to monitor tumour response via MRI and to assess whether treatment should continue or stop. New medications are expected to reduce tumour size, improve patient quality of life, and provide lasting benefits, all while maintaining manageable side effects. Mild to moderate side effects like rashes or gastrointestinal issues are considered acceptable, but severe adverse events should be minimized, with clear protocols for monitoring and managing any toxicities.

Given the evolving understanding of NF1-associated PNs, there is also a need to address unmet medical needs, especially for adults and those who experience significant side effects from existing treatments. Mirdametinib could serve as an alternative option for such patients. Off-label treatments also offer potential benefits, though they carry risks of their own, including liver or kidney toxicity. As new drugs are developed, they must balance efficacy with safety to ensure long-term tumour control and enhanced patient well-being. In addition, the risks associated with treating pregnant patients or those of child-bearing potential require particular caution, as MEK inhibitors may pose foetal risks. Careful monitoring and timing of treatment are critical to ensure both maternal and foetal safety. Overall, new treatments must aim to broaden patient eligibility, reduce resistance risks, and offer sustained improvements in managing PNs while maintaining manageable side effects.

2.6.6. Discussion on clinical efficacy

The initially sought indication within this marketing authorisation application was:

Ezmekly as monotherapy is indicated for the treatment of adult and paediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).

The application is mainly based on an ongoing open-label, single arm, multi-centre phase I/II study in adult and paediatric participants with NF1-Associated Plexiform Neurofibromas (study MEK-NF-201).

The applicant also provided the result of a completed phase II study in adult and adolescent participants with NF1-Associated Plexiform Neurofibromas (study NF-106).

Additionally, the applicant used as external control data:

- Data from patients included in the placebo arm of a tipifarnib randomised placebo-controlled study which has been conducted by the National Cancer Institute in participants with NF1 and progressive PN (Study 01 C-0222)
- Data from a Natural History non interventional prospective study which has been conducted by the National Cancer Institute (study 08-C-0079).

The applicant did not conduct a proper dose response study. In clinical studies in advanced cancer, mirdametinib was assessed at dose levels doses between 2 and 10 mg BID with an intermittent schedule. The chosen dose for NF1 is based on non-clinical data in a NF1 mouse model and PD data showing that doses ≥ 2 mg BID caused ≥ 60% suppression of phosphorylated ERK in tumour biopsies of adult with melanoma.

Design and conduct of clinical studies

Study MEK-NF-201 (pivotal study):

The pivotal study MEK-NF-201 was an open-label and single arm phase IIb study conducted to determine the efficacy and safety of mirdametinib in participants ≥2 years old with symptomatic inoperable NF1-associated PNs.

The absence of a randomised comparator and the exploratory nature of such trial design are obvious limitations to the interpretation of the study results. It is acknowledged that the natural course of PNs is growth or at best stable over time, therefore, objective responses observed in the pivotal study could in principle be attributed to study treatment. Nevertheless, in the context of a highly heterogeneous disease, the single arm design (and its absence of a concurrent control) leads to uncertainties regarding the exact effect that can be attributed to treatment.

Patients who participated in this study had at least one Plexiform neurofibroma (PN) which causes significant morbidity, such as (but not limited to) airway or great vessels compression, nerve compression and loss of function, major deformity or significant disfiguring, and painful lesion. There were no inclusion/exclusion criteria regarding the location of the PN or the associated morbidity. The inclusion was not limited to patients with progressive PN. Participant who previously received or was currently receiving therapy with mirdametinib or any other MEK1/2 inhibitor (e.g. selumetinib, trametinib, cobimetinib, binimetinib, etc.) were excluded.

For this study, the applicant developed 2 different formulations with different dosages:

- a capsule formulation that contains either 1 or 2 mg of mirdametinib
- a tablet formulation, which can either be swallowed whole or dispersed in water and administered as an oral suspension, which contains either 0.5 or 1 mg of mirdametinib.

During the study, patients had the option to take either formulation depending on their preference.

The starting dose was 2 mg/m2 BID (approximately every 12 hours without regard to food), using an intermittent regimen (3 weeks on/1 week off) in 28-day cycles. Dosing was interrupted and/or dose reduced in the event of significant toxicity.

Dosing was based on different nomograms specific for tablets (0.5 and 1 mg) or capsules (1 and 2 mg). Compared to capsules, tablets allow a more refined adaptation of dosage based on body surface area, and also allow smaller dose reduction steps. As a result, the posology based on body surface area and dose reduction regimens were different depending on the dosage formulation.

No marketing authorisation is requested for the 0.5 mg tablet formulation and a unified nomogram is proposed in the PI for both the capsule and tablet formulations.

The duration of treatment during the Treatment Phase was 2 years; participants had the possibility to enter an optional Long-Term Follow-Up Phase.

All tumour volume measurements were based on a BICR including two readers, as well as an independent adjudicator providing the final decision in case of disagreement. Although the performance of an independent central review is appreciated in the context of a SAT, the procedure (as described in the imaging review charter) is found not to be optimal. Indeed, for prospective reads, the central reviewers were displayed time points in chronological order and in an incremental mode. For retrospective reads, the central reviewers read one participant's time points in chronological order and were allowed to access all prior time points. The readers were not blinded to the patients' time point, but only to the participant's protected health information and to the exact study visit (which could be at least partially guessed from the chronological ordering). Despite these limitations, a similar

independent review procedure was followed in the assessment of another product in the same indication and ultimately deemed acceptable.

Given that independent central review process was modified with the addition of a second reader and of an adjudicator, the sensitivity analyses by each BICR reader allow for some consistency assessment against the initial plan.

The primary objective of the study was to evaluate the confirmed Objective Response Rate (ORR) at the end of the Treatment Phase.

The primary endpoint was defined as the percentage of patients with confirmed complete response (CR) or partial response (PR), with PR defined as target Plexiform Neurofibroma (PN) volume decrease ≥20% at the end of the Treatment Phase compared to baseline. Responses were considered confirmed if the PR was maintained at the subsequent MRI within the 2 to 6 months. Evolution in target PN volume compared to baseline was assessed by a blinded independent central reviewer (BICR) in order to minimize investigator bias. Overall, the primary endpoint ORR is considered acceptable. However, ORR should be related to a functional clinical outcome and the use of 3D-volumetric MRI for tumour measurements and the 20% reduction of the tumour volume are in line with the REiNS recommendations for imaging tumour response in neurofibromatosis clinical trials (Dombi et al. 2013) which have been previously accepted by the CHMP (Koselugo EPAR).

The secondary and tertiary endpoints covered a wide range of clinical outcomes, as symptoms may vary based on the location and extent of PN. Therefore, the use of multiple clinical outcomes which are considered critical to demonstrate the clinical relevance of the observed tumour reduction is agreed. However, the interpretability of the endpoints was hampered by the open-label design, the lack of a comparator treatment arm and the small sample size.

Moreover, the interpretation of endpoints based on patient reported outcomes (PRO) is problematic in SATs as the absence of blinding adds to the uncertainty related to having no comparator. Time-to-event endpoints (such as TTP and PFS) are also particularly challenging to assess in single arm designs without the internal calibration of a comparator arm.

In order to address the limitations associated with the SAT design of the pivotal trial, the applicant has provided a set of exploratory analyses comparing adult and paediatric patients treated with mirdametinib to external historical controls, including study 08-C-0079 (a natural history study of participants with NF1) and the placebo arm of study 01-C-0222. Nevertheless, these exploratory comparisons to external controls have inherent limitations and uncertainties, which are further discussed below.

There were several important changes made to the planned analyses in the statistical analysis plan (SAP) in comparison with the protocol. The applicant clarified that changes were implemented before database lock. However, the late implementation of key modifications further highlights the exploratory nature of this SAT.

In particular, the null hypothesis for paediatric patients in the study protocol (and also used for sample size considerations) was that the ORR is less than or equal to 42%. This clinical threshold for the paediatric cohort was updated, with a revised hypothesis test comparing the observed ORR to a new reference threshold of 20%. It is noted that the primary ORR analysis would not have been successful under the original hypothesis test making use of the 42% reference threshold (as the lower confidence limit is below 42%). This modification followed the availability of the centrally reviewed 44% ORR result from the SPRINT study, in comparison with the 66% ORR per its initial single reading. The applicant indicated that the change in null hypothesis for the paediatric population was proposed to the FDA approximately one year before database lock. Nevertheless, in the context of an open-label single-

arm trial, it is generally difficult to exclude some level of (partially) informed decisions for any changes introduced while the study is ongoing.

Although the reference threshold for the hypothesis test of the adult cohort was not modified, in the absence of a concurrent control, such hypothesis test against a fixed reference threshold is considered of exploratory nature.

Another important change to the planned analyses was the addition of a second reader to the BIRC, and, in the case of a difference in response status, the use of an independent adjudicator to make the final determination.

There was no multiplicity adjustment between paediatric and adult populations, considered as independent cohorts, nor across primary and secondary endpoints. Both cohorts were enrolled in parallel and had separate success criteria, with no planned hierarchical testing procedure.

The DoR analysis, as specified in the protocol, is not in line with the REiNS criteria. Nevertheless, sensitivity analyses based on the REiNS criteria were provided (data not shown).

The DoR, PFS and TTP analyses are also not fully in line with EMA guidance *Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials* (EMA/CHMP/27994/2008/Rev.1). Indeed, it would have been preferred that all available measurements were used for analyses, regardless of missing/inadequate assessments and regardless of subsequent therapy or surgery. However, it is acknowledged that very few patients were censored for these reasons (at most 1 patient in either category, depending on the analysis considered). Therefore, this issue is not thought to have had a meaningful impact on study results, and was not further pursued.

Given the limitations of PRO data in the context of SATs, additional analyses looking at the impact of missing data were considered of limited added value and therefore not requested.

Supportive study NF-106

It is a single arm phase II study sponsored by the University of Alabama at Birmingham.

The NF-106 study aimed to include adolescent and adult participants aged 16 years and older with NF1 and morbid or progressing PNs.

For this study only the 1 mg hard capsule was provided.

The primary objective was to assess the tumour response using centrally read MRI. Tumour response was as defined as decrease in tumour volume from baseline of at least 20% at Cycle 12.

Comparisons to external control data

Two historical controls were included in these analyses: the placebo control arm of the study 01-C-0222 and the natural history study 08-C-0079; both studies were conducted by the National Cancer Institute.

The comparisons of MEK-NF-201 efficacy endpoints to external control data were not pre-specified in the study protocol. Indeed, the only mention of such analyses was the inclusion of an exploratory/tertiary objective which was "to assess TTP of mirdametinib versus historical controls". There was no separate objective of external comparisons for the percentage change in TN volume or PFS, and there were no details provided for the selection of historical controls nor for any planned statistical analyses and covariate adjustment.

Therefore, these exploratory analyses performed for external control comparisons were entirely defined in a SAP addendum, dated 31 October 2023, hence finalised after the data cut-off date (20 September 2023) of the pivotal single-arm trial. In this situation, it cannot be excluded that several aspects of the planned analyses (historical data sets and selection criteria, endpoint selection and definition, propensity score weighting/matching methods and associated covariates, planned statistical models and adjustment…) could be at least partially data driven. The lack of pre-specification is a clear limitation of these external control comparisons. This issue, unfortunately, cannot be resolved retrospectively.

It is noted that the estimand framework, which has not been used for the main analyses of the pivotal trial, has not been followed for these external control comparisons either. It would have been helpful to conceptually define the clinical questions of interest for these comparisons, by clearly defining estimand attributes and the handling of intercurrent events.

There were only a few baseline variables used for propensity score matching / weighting. Age, lesion type (distinct nodular lesion or solitary nodular vs. other) and prior MEK inhibitor treatment (3 variables) were used for matching / weighting against study 08-C-0079, and only age was used for study 01-C-0222 due to the unavailability of the other two variables. It is unclear how these variables were identified as the most prognostic factors for propensity scores, and why there were no other baseline characteristics considered for inclusion in their derivation. As a consequence, it is highly likely that other relevant prognostic factors (known or unknown) were not accounted for and may have biased the estimates of external control comparisons.

In order to ensure the consistency of outcome assessments across the data sets used for external control comparisons, a blinded independent central review (BICR) should have been ideally performed, similarly to the one performed for the pivotal trial, in order to minimize any bias related to differences in assessment procedures (and ideally, blinded to both treatment and time point). The difficulties in implementing such retrospective exercise in historical datasets is acknowledged, but the additional uncertainty related to this issue should be considered.

As acknowledged by the applicant, missing data were not imputed, and no sensitivity analyses were performed to assess the potential impact of missing data on the results.

Even when prospectively performed with well-matched patient populations, similar patient follow-up and consistent endpoint derivations across data sets, comparisons to external controls have inherent limitations, as some remaining bias can be difficult to rule out due to the potential presence of unknown confounders. All above considerations (including the absence of pre-specification, the few prognostic factors accounted for in propensity score methods and the lack of missing data handling) are additional limitations to these exploratory analyses. Given the numerous sources of possible bias, results should be interpreted with caution, particularly regarding the exact size of estimated treatment effects.

Efficacy data and additional analyses

Study NEF MEK 201-pivotal

A total of 114 patients were included, 56 paediatrics and 58 adults. Overall, 19 (33.9%) and 27 (46.6%) participants discontinued the treatment before completing the treatment phase. The most frequent reason was progressive disease in the paediatric cohort and AEs in the adult cohort.

Among patients eligible for the LTFU phase, 28 (84.8%) and 26 (83.9%) entered the LTFU respectively.

In the paediatric cohort, ages of the children at the enrolment ranged from 2 to 17 years. Female represented 54% of the population. White subjects (66%) were the most presented patients. In the

adult cohort, the mean age at entry was 35.0 years, ranging from 18 to 69 years. Female represented 64% of the population. White subjects (85%) were the most presented patients.

In both cohorts around half of the patients had their target PN location in the head and neck, and 31 (53.4%) and 35 (63%) of adult and paediatric patients, respectively, had a progressing PN at inclusion. The most prevalent target PN morbidities were pain, disfigurement or major deformity and motor dysfunction in both cohorts.

A total of 25 (45%) patients in the paediatric cohort and 43 (74%) patients in the adult cohort had at least 1 prior PN therapy.

In general, the included patient population is considered an acceptable reflection of the patient population targeted by the indication applied for.

Although the study exclusion criteria stipulated that patients should not receive or have received MEK inhibitor, six (11%) participants in the paediatric cohort and four (7%) participants in the adult cohort received prior MEK inhibitor therapy. The most common prior MEK inhibitors therapy were selumetinib and trametinib. A sensitivity analysis excluding patients who previously received a MEK1/2 inhibitor were consistent with the main analysis (data not shown).

Primary endpoint - Response rate:

No patients had a complete response i.e. full regression of the target plexiform neurofibroma (PN).

The confirmed ORR was 51.8 % (95% IC 38.0, 65.3) in the paediatric cohort and 44.1% (95% IC 28.6, 55.1) in the adult cohort.

It is also noted that the ORR 95% CI ranges from 38.0% to 65.3% in the paediatric cohort and from 28.6% to 55.1% in the adult cohort. This is probably due/related to the relatively small sample size but nevertheless is considered to carry an important level of uncertainty toward the activity of mirdametinib.

Due to the late modification of the null hypothesis for paediatric patients in the study protocol the p-value is not considered relevant.

Secondary endpoints- Duration of response

The median DoR was not reached for the paediatric cohort neither for the adult cohort.

It should be noted that the study is ongoing the applicant will provide data from the extension phase, as a specific obligation (SOB).

The applicant provided updated data with 9 additional months of follow-up. These updated data showed a sustained treatment effect from mirdametinib with additional confirmed responses observed in the LTFU phase, observed responses remaining durable, and a larger proportion of responders maintaining a confirmed response for ≥12 months.

Secondary endpoints- Clinical outcomes (COAs)

Clinical secondary endpoints were assessed as changes from baseline to -Cycle 13 i.e. after approximately 12 months of treatment.

The effect on quality of life, assessed through the PedsQL, showed an improvement both in adult and in paediatric cohorts.

The pain assessed through the NRS-11, and the influence of pain on daily functioning assessed through the PII showed an improvement both in adult and in paediatric cohorts.

No clear positive relationship was observed between tumour response and improvement in quality of life or pain. Depending on the endpoints and the adult or paediatric population, the improvement in pain is more marked in non-responders than in responders. Similarly, the results on improvement in quality of life do not seem to correlate with the reduction in tumour size.

However, the limited number of patients and the absence of control arm limits the interpretability of these results.

Supportive study NF-106

In 6 out of 19 participants, the best overall confirmed response total was PR no participants had a CR. The ORR for the total population was 31.6% (95% CI: 12.58, 56.55; p<0.001).

The median (min, max) best percentage change from baseline in target tumour volume was -17.14% (-28.0, 17.9).

Efficacy results were in line with those of the pivotal study. However, the same limitations as those highlighted in the pivotal study also apply, such as the fact that this is an open-label study with no comparator arm, the small number of participants and the lack of long-term data on the primary endpoint.

Comparisons to external control data

Comparisons of paediatric participants (age 2 to <18 years) with progressive PN at baseline showed in improvement in yearly percentage change from baseline in target PN volume, TTP, and PFS in study MEK-NF-201 compared to study 01-C-0222.

Comparisons of paediatric patients (age 2 to <18 years) showed an improvement in yearly percentage change from baseline in target PN volume, TTP, and PFS in study MEK-NF-201 compared to study 08-C-0079 (data not shown).

Comparisons of adult participants showed an improvement in yearly percentage change from baseline in target PN volume in study MEK-NF-201 compared to study 08-C-0079.

Both external controls could provide some useful context data, however considering the heterogeneity of the baseline populations (age, disease progression, tumour volume) and the possible identified bias, it is difficult to carry out relevant comparative analyses between these 2 external controls and the pivotal study.

Wording of the indication:

During the procedure, the applicant was requested to amend the wording of the indication in order to further align with other currently authorised products. The final indication included in section 4.1 of the SmPC is:

Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

Additional efficacy data needed in the context of a conditional MA

Considering the rarity of the disease and the absence of relevant comparator beyond Koselugo (currently under CMA and only authorised for patients aged between 3 and 18 years), having a single arm trial as pivotal evidence was deemed acceptable for the assessment of the benefit-risk.

Due to the methodological limitations associated with a SAT, the efficacy of the treatment was based on response rate and in such context, adequate description of the duration of response is necessary to characterise the treatment effect. In the current application, the median duration was not yet reached

and is considered necessary to achieve comprehensiveness of the data package. As such, provision of an additional 5 years of follow-up from the pivotal study is requested as a specific obligation, in order to fully characterise the duration of response, and to confirm the long term benefit of mirdametinib in patients responding to treatment.

2.6.7. Conclusions on the clinical efficacy

The efficacy package is mostly based on a small open label uncontrolled study, using as primary endpoint a confirmed objective responses rate (ORR), defined as PN decrease ≥ 20% compared to baseline in consecutive scans within 2-6 months. Results showed a confirmed ORR (95% CI) of 51.8% (38.0, 65.3) in the paediatric cohort and 41.4% (28.6, 55.1) in the adult cohort. However, no clear correlation was observed between change in patients reported outcomes and change in target PN volume. Considering that NF1 is a rare disease and since the target population is limited to NF1 patients with symptomatic PN, recruiting a large number of participants in a study would be challenging. Moreover, the natural evolution of PN is growth or, at most, stable over time, so any observed objective response in the pivotal study can in principle be attributed to mirdametinib. However, the durability of the decrease in target PN volume is uncertain as long-term data of the pivotal study were not provided.

The CHMP considers the following measure necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of mirdametinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should submit an updated analysis of the study MEK-NF-201 with a data cut-off of 22 December 2028 that will provide an additional 5 years of follow-up.

2.6.8. Clinical safety

The safety profile of mirdametinib is based on the pivotal study, MEK-NF-201, and on a phase 2 investigator-initiated study, NF-106. As supportive data, two other studies in patients with advanced cancer were also submitted, study A4581001 and study A4581002.

These 4 studies were grouped into the following pools based on the targeted underlying condition, NF1 PN or advanced cancers, dosing regimen (body surface area vs unit dosing), participants, and study design:

▪ The **pool 1** integrating safety data from studies MEK-NF-201 and NF-106 in adult and paediatric participants with NF1 PN. The data were analysed together as a single pool and are the primary safety data used to assess the safety profile of mirdametinib in adult and paediatric participants with NF1 PN.

Study MEK-NF-201: a total of 114 patients: 58 adults and 56 paediatric ≥2 years are included in this study and. The data cut-off date used for the primary analysis in the clinical study report (CSR) and the summary of clinical safety was 20 September 2023. This study is still ongoing.

Study NF-106: nineteen patients were enrolled, 17 adults and 2 paediatric ≥ 16 years. This study ended on 9 August 2017.

▪ The **pool 2** integrating safety data from studies A4581001 and A4581002 in adult participants with advanced cancers. These data were analysed together as a single pool and are supportive safety data.

Of note, eleven additional trials were submitted as supplementary data but the information provided is limited.

Since mirdametinib MAA is intended for patients with NF1-associated inoperable NF, data from pool 1 was used as the primary safety data and is presented below.

2.6.8.1. Patient exposure

Table 32: Participant disposition for pool 1 – MEK-NF-201 and NF-106

	Pool 1		
	Paediatric NF1 PN 2mg/m² BID (N=58)	**Adult NF1 PN 2mg/m² BID (N=75)**	**Total NF1 PN 2mg/m² BID (N=133)**
Number of Participants Who Received At least One Dose	58 (100%)	75 (100%)	133 (100%)
MEK-NF-201	56 (96.6%)	58 (77.3%)	114 (85.7%)
NF-106	2 (3.4%)	17 (22.7%)	19 (14.3%)
Number of Participants Who Completed the Study Treatment	34 (58.6%)	36 (48.0%)	70 (52.6%)
Number of Participants Who are Ongoing Study Treatment	4 (6.9%)	0	4 (3.0%)
Number of Participants Discontinued from Study Treatment	20 (34.5%)	39 (52.0%)	59 (44.4%)
Primary Reason for Discontinuation from Study Treatment			
Progressive Disease	9 (15.5%)	4 (5.3%)	13 (9.8%)
Lack of Efficacy	0	6 (8.0%)	6 (4.5%)
Participant Decision	5 (8.6%)	11 (14.7%)	16 (12.0%)
Participant Non-Compliance	2 (3.4%)	3 (4.0%)	5 (3.8%)
Physician/Sponsor Decision	0	0	0
Adverse Event	4 (6.9%)	14 (18.7%)	18 (13.5%)
COVID-19	0	0	0
Other	0	1 (1.3%)	1 (0.8%)

BID: twice daily; LTFU: Long-Term Follow-Up; m: meter; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator (N).
Note: At the time of the data cutoff some participants who completed treatment phase in MEK-NF-201 are still ongoing in LTFU.

Table 33: Patient exposure from pool 1– MEK-NF-201 and NF-106

	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Duration of Mirdametinib Exposure (Months)			
N	58	75	133
Mean (StD)	20.86 (10.690)	18.04 (13.002)	19.27 (12.087)
Median	21.87	18.66	21.85

	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Min, Max	1.6, 40.1	0.4, 45.6	0.4, 45.6
Total Duration of Exposure (years) for all Participants	100.8	112.7	213.5
Number of Participants who Received Study Treatment			
For at least 1 month	58 (100%)	70 (93.3%)	128 (96.2%)
For at least 2 months	57 (98.3%)	68 (90.7%)	125 (94.0%)
For at least 3 months	56 (96.6%)	68 (90.7%)	124 (93.2%)
For at least 6 months	51 (87.9%)	60 (80.0%)	111 (83.5%)
For at least 12 months	42 (72.4%)	41 (54.7%)	83 (62.4%)
For at least 24 months	24 (41.4%)	26 (34.7%)	50 (37.6%)
For at least 36 months	6 (10.3%)	10 (13.3%)	16 (12.0%)
Number of Participants Receiving All Planned Doses	18 (31.0%)	27 (36.0%)	45 (33.8%)
Participants With at least 1 Dose Modification	40 (69.0%)	48 (64.0%)	88 (66.2%)
Time to Dose Modification (Months)			
n	40	48	88
Mean (StD)	7.37 (6.673)	5.96 (8.939)	6.60 (7.977)
Median	4.24	1.37	3.57
Min, Max	0.0, 21.6	0.0, 44.8	0.0, 44.8
Participants With at least 1 Dose Reduction due to a TEAE	7 (12.1%)	15 (20.0%)	22 (16.5%)
Time to Dose Reduction (Months)			
n	7	9	16
Mean (StD)	3.45 (4.734)	5.09 (6.319)	4.37 (5.565)
Median	1.74	1.22	1.48
Min, Max	0.3, 13.9	0.3, 14.4	0.3, 14.4
Participants With at least 1 Dose Interruption	17 (29.3%)	21 (28.0%)	38 (28.6%)
Interruption Due to a TEAE	17 (100%)	21 (100%)	38 (100%)
TEAE Related to Study Treatment	8 (47.1%)	7 (33.3%)	15 (39.5%)

	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Time to Dose Interruption (Months)			
n	17	21	38
Mean (StD)	9.43 (8.654)	11.65 (12.901)	10.66 (11.118)
Median	7.10	5.65	6.03
Min, Max	0.3, 26.8	0.1, 44.7	0.1, 44.7
Participants With Treatment Discontinuation Due to TEAE	5 (8.6%)	16 (21.3%)	21 (15.8%)
Related to Study Treatment	5 (100%)	15 (93.8%)	20 (95.2%)

BID: twice daily; m: meter; Max: Maximum; Min: Minimum; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; QD: once daily; StD: Standard deviation; TEAE: Treatment-Emergent Adverse Event.
Dose group is based on the assigned dose at baseline. Planned dose is defined as the assigned dose at baseline.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator.
Subcategories, shown by an indent, use the number of participants in the category as the denominator.
Dose reduction is defined as re-assignment of dose where the new dose is less than the original dose assigned at baseline as a result of an AE.
Dose interruption is based on the information recorded in dosing records or as a result of an AE.
Dose modification is defined as dose reduction, or dose interruption, or dose discontinuation.
Participants can have multiple reasons for dose modifications, reductions, or interruptions, and thus can be counted in multiple rows corresponding to reasons.
Duration of study exposure in months is calculated as (last dose date – first dose date +1)/30.4375.
Time to dose modification/reduction/interruption in months are calculated as (dose modification/reduction/interruption date – first dose date +1)/ 30.4375. Dose reduction is based on dosing records.

2.6.8.2. Adverse events

Table 34: Overall AE profile for pool 1 - MEK-NF-201 and NF-106

	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Number of Participants with at least one TEAE	58 (100%)	75 (100%)	133 (100%)
Number of Participants with at least one Treatment-related TEAE	55 (94.8%)	74 (98.7%)	129 (97.0%)
Number of Participants with at least one SAE	8 (13.8%)	12 (16.0%)	20 (15.0%)
Number of Participants with at least one Treatment-related SAE	0	3 (4.0%)	3 (2.3%)
Number of Participants with at least one TEAE in Safety Topic of Interest	57 (98.3%)	75 (100%)	132 (99.2%)

	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Number of Participants with at least one Treatment-related TEAE in Safety Topic of Interest	51 (87.9%)	73 (97.3%)	124 (93.2%)
Number of Participants with at least one Grade 3 or Above TEAE	23 (39.7%)	26 (34.7%)	49 (36.8%)
Maximum Intensity of TEAE			
Grade 1	8 (13.8%)	9 (12.0%)	17 (12.8%)
Grade 2	27 (46.6%)	40 (53.3%)	67 (50.4%)
Grade 3	21 (36.2%)	23 (30.7%)	44 (33.1%)
Grade 4	2 (3.4%)	2 (2.7%)	4 (3.0%)
Grade 5	0 (0.0%)	1 (1.3%)	1 (0.8%)
Number of Participants with at least one Grade 3 or Above Treatment-related TEAE	14 (24.1%)	11 (14.7%)	25 (18.8%)
Number of Participants with at least one Grade 3 or Above TEAE in Safety Topics of Interest	15 (25.9%)	16 (21.3%)	31 (23.3%)
Number of Participants with at least one TEAE Leading to Study Discontinuation	4 (6.9%)	12 (16.0%)	16 (12.0%)
Number of Participants with at least one TEAE Leading to Mirdametinib Discontinuation	5 (8.6%)	16 (21.3%)	21 (15.8%)

AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NCI: National Cancer Institute; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas. SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event.
TEAE = an AE that starts or worsens on or after the first dose of study treatment, including those occurring or increasing in severity up to 30 days after the last dose of study treatment
All AEs are coded using MedDRA Version 24.0.
AE severity was graded using NCI-CTCAE Version 5.0: 1=Mild; 2=Moderate; 3=Severe; 4=Life-Threatening; 5=Death.
Dose group is based on the assigned dose at baseline.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator (N).

Table 35: TEAEs leading to discontinuation from pool 1 - MEK-NF-201 and NF-106

	Pool 1		
	Pediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Number of Participants with at least one TEAE Leading to Study Discontinuation	4 (6.9%)	12 (16.0%)	16 (12.0%)
Number of Participants with at least one TEAE Leading to Mirdametinib Discontinuation	5 (8.6%)	16 (21.3%)	21 (15.8%)

AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NCI: National Cancer Institute; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas. SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event.
TEAE = an AE that starts or worsens on or after the first dose of study treatment, including those occurring or increasing in severity up to 30 days after the last dose of study treatment
All AEs are coded using MedDRA Version 24.0. Safety topics of interest are defined in ISS SAP Section 6.4.1.2.
AE severity was graded using NCI-CTCAE Version 5.0: 1=Mild; 2=Moderate; 3=Severe; 4=Life-Threatening; 5=Death.
Dose group is based on the assigned dose at baseline.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator (N).

Table 36: Incidence of frequently (≥15% of participants in any group) occurring TEAEs in participants who received mirdametinib (descending order) - pool 1 - MEK-NF-201 and NF-106

Preferred Term	Pool 1		
	Paediatric NF1 PN 2 mg/m^2 BID (N=58)	Adult NF1 PN 2 mg/m^2 BID (N=75)	Total NF1 PN 2 mg/m^2 BID (N=133)
Number of Participants with at least one TEAE	58 (100%)	75 (100%)	133 (100%)
Dermatitis acneiform	25 (43.1%)	62 (82.7%)	87 (65.4%)
Diarrhoea	31 (53.4%)	41 (54.7%)	72 (54.1%)
Nausea	17 (29.3%)	41 (54.7%)	58 (43.6%)
Vomiting	23 (39.7%)	28 (37.3%)	51 (38.3%)
Fatigue	7 (12.1%)	27 (36.0%)	34 (25.6%)
Headache	21 (36.2%)	12 (16.0%)	33 (24.8%)
Abdominal pain	16 (27.6%)	12 (16.0%)	28 (21.1%)
COVID-19	14 (24.1%)	13 (17.3%)	27 (20.3%)
Blood creatine phosphokinase increased	14 (24.1%)	11 (14.7%)	25 (18.8%)
Ejection fraction decreased	15 (25.9%)	9 (12.0%)	24 (18.0%)
Pain in extremity	12 (20.7%)	12 (16.0%)	24 (18.0%)
SARS-CoV-2 test positive	11 (19.0%)	12 (16.0%)	23 (17.3%)
Paronychia	19 (32.8%)	2 (2.7%)	21 (15.8%)
Dizziness	5 (8.6%)	16 (21.3%)	21 (15.8%)
Arthralgia	9 (15.5%)	12 (16.0%)	21 (15.8%)
Dry skin	10 (17.2%)	10 (13.3%)	20 (15.0%)
Constipation	6 (10.3%)	14 (18.7%)	20 (15.0%)
Cough	13 (22.4%)	6 (8.0%)	19 (14.3%)
Upper respiratory tract infection	15 (25.9%)	1 (1.3%)	16 (12.0%)
Weight increased	9 (15.5%)	7 (9.3%)	16 (12.0%)
Rash	11 (19.0%)	4 (5.3%)	15 (11.3%)
Pyrexia	11 (19.0%)	4 (5.3%)	15 (11.3%)
Abdominal pain upper	9 (15.5%)	3 (4.0%)	12 (9.0%)

AE: Adverse Event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.

All TEAEs are coded using MedDRA Version 24.0.
Each participant is counted only once within each system organ class and preferred term if they experience an AE with that system organ class and preferred term more than once.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Table 37: Incidence of grade ≥3 TEAEs occurring in ≥2 participants in any group who received mirdametinib (descending order) - pool 1 - MEK-NF-201 and NF-106

Preferred Term	Pool 1		
	Paediatric NF1 PN 2 mg/m² BID (N=58)	**Adult NF1 PN 2 mg/m² BID (N=75)**	**Total NF1 PN 2 mg/m² BID (N=133)**
Number of Participants with at least one TEAE of at Least Grade 3 Severity	23 (39.7%)	26 (34.7%)	49 (36.8%)
Dermatitis acneiform	1 (1.7%)	5 (6.7%)	6 (4.5%)
Blood creatine phosphokinase increased	4 (6.9%)	1 (1.3%)	5 (3.8%)
Neutrophil count decreased	5 (8.6%)	0	5 (3.8%)
Abdominal pain	2 (3.4%)	3 (4.0%)	5 (3.8%)
Syncope	3 (5.2%)	1 (1.3%)	4 (3.0%)
Weight increased	2 (3.4%)	1 (1.3%)	3 (2.3%)
Diarrhoea	3 (5.2%)	0	3 (2.3%)
COVID-19	0	3 (4.0%)	3 (2.3%)
Back pain	0	3 (4.0%)	3 (2.3%)
SARS-CoV-2 test positive	0	2 (2.7%)	2 (1.5%)
Headache	1 (1.7%)	1 (1.3%)	2 (1.5%)
Pain in extremity	1 (1.7%)	1 (1.3%)	2 (1.5%)
Nephrolithiasis	0	2 (2.7%)	2 (1.5%)

Table 38: Incidence of frequently (≥5% of participants in any group) occurring treatment-related TEAEs in participants who received mirdametinib (in descending order of frequency by the Total column) - pool 1 - MEK-NF-201 and NF-106

Preferred Term	Pool 1		
	Pediatric NF1 PN 2 mg/m2 BID (N=58)	Adult NF1 PN 2 mg/m2 BID (N=75)	Total NF1 PN 2 mg/m2 BID (N=133)
Participants With at least One Treatment-Related TEAE	55 (94.8%)	74 (98.7%)	129 (97.0%)
Dermatitis acneiform	25 (43.1%)	62 (82.7%)	87 (65.4%)
Diarrhoea	21 (36.2%)	34 (45.3%)	55 (41.4%)
Nausea	13 (22.4%)	31 (41.3%)	44 (33.1%)
Vomiting	8 (13.8%)	21 (28.0%)	29 (21.8%)
Fatigue	5 (8.6%)	22 (29.3%)	27 (20.3%)
Blood creatine phosphokinase increased	13 (22.4%)	9 (12.0%)	22 (16.5%)
Paronychia	18 (31.0%)	2 (2.7%)	20 (15.0%)
Ejection fraction decreased	11 (19.0%)	7 (9.3%)	18 (13.5%)
Alopecia	7 (12.1%)	9 (12.0%)	16 (12.0%)
Dry skin	8 (13.8%)	8 (10.7%)	16 (12.0%)
Abdominal pain	8 (13.8%)	5 (6.7%)	13 (9.8%)
Pruritus	3 (5.2%)	8 (10.7%)	11 (8.3%)
Rash	7 (12.1%)	4 (5.3%)	11 (8.3%)
Constipation	3 (5.2%)	8 (10.7%)	11 (8.3%)
Weight increased	8 (13.8%)	3 (4.0%)	11 (8.3%)
Dizziness	2 (3.4%)	9 (12.0%)	11 (8.3%)
Headache	6 (10.3%)	3 (4.0%)	9 (6.8%)
Eczema	6 (10.3%)	2 (2.7%)	8 (6.0%)
Abdominal pain upper	6 (10.3%)	2 (2.7%)	8 (6.0%)
Stomatitis	5 (8.6%)	3 (4.0%)	8 (6.0%)
Hair colour changes	6 (10.3%)	1 (1.3%)	7 (5.3%)
Urticaria	3 (5.2%)	4 (5.3%)	7 (5.3%)
Oedema peripheral	2 (3.4%)	5 (6.7%)	7 (5.3%)
Dry mouth	0	5 (6.7%)	5 (3.8%)
Neutrophil count decreased	5 (8.6%)	0	5 (3.8%)
Rash pustular	4 (6.9%)	1 (1.3%)	5 (3.8%)
Hypocalcaemia	3 (5.2%)	2 (2.7%)	5 (3.8%)
Pain in extremity	3 (5.2%)	2 (2.7%)	5 (3.8%)
Anaemia	1 (1.7%)	4 (5.3%)	5 (3.8%)
Hair texture abnormal	3 (5.2%)	1 (1.3%)	4 (3.0%)
White blood cell count decreased	3 (5.2%)	1 (1.3%)	4 (3.0%)
Hypertriglyceridaemia	4 (6.9%)	0	4 (3.0%)

Reference: Table 14.3.2.5.1.

AE: Adverse Event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.

All TEAEs are coded using MedDRA Version 24.0.

Each participant is counted only once within each system organ class and preferred term if they experience an AE with that system organ class and preferred term more than once.

An AE is classified as related to study treatment if it has an Investigator determination of related to study treatment.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Table 39: Incidence of grade ≥3 treatment-related TEAEs occurring in participants who received mirdametinib (in descending order of frequency by the total column) - pool 1 - MEK-NF-201 and NF-106

Preferred Term	Pool 1		
	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Number of Participants with at least one Related TEAE of at Least Grade 3 Severity	14 (24.1%)	11 (14.7%)	25 (18.8%)
Dermatitis acneiform	1 (1.7%)	5 (6.7%)	6 (4.5%)
Blood creatine phosphokinase increased	4 (6.9%)	1 (1.3%)	5 (3.8%)
Neutrophil count decreased	5 (8.6%)	0	5 (3.8%)
Abdominal pain	2 (3.4%)	1 (1.3%)	3 (2.3%)
Weight increased	2 (3.4%)	0	2 (1.5%)
Ejection fraction decreased	1 (1.7%)	0	1 (0.8%)
Rash	1 (1.7%)	0	1 (0.8%)
Rash erythematous	0	1 (1.3%)	1 (0.8%)
Abdominal pain upper	1 (1.7%)	0	1 (0.8%)
Diarrhoea	1 (1.7%)	0	1 (0.8%)
Back pain	0	1 (1.3%)	1 (0.8%)
Pain in extremity	1 (1.7%)	0	1 (0.8%)
Retinal vein occlusion	0	1 (1.3%)	1 (0.8%)
Fatigue	0	1 (1.3%)	1 (0.8%)

Reference: Table 14.3.2.11.1.

AE: Adverse event; BID: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NCI: National Cancer Institute; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; TEAE: Treatment-Emergent Adverse Event.

All TEAEs are coded using MedDRA Version 24.0.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

All AEs are graded for severity using NCI-CTCAE Version 5.0: 1=Mild; 2=Moderate; 3=Severe; 4=Life-threatening; 5=Death.

Adverse drug reactions

Adverse drug reactions (ADRs) for mirdametinib were defined as those AEs considered related to mirdametinib based on the assessment of numerical frequency data and review of individual case details such as temporal association of the event with administration of mirdametinib, dechallenge and rechallenge information, and confounding factors such as intercurrent illnesses and administration of concomitant medications which could be plausible alternative causes for the reported events. The presence of a description of a plausible mechanism by which MEK inhibition could lead to the reported event in the literature was also taken into account when considering if a reported event was an adverse reaction for mirdametinib.

Based on the totality of the data, AEs that are considered ADRs for mirdametinib in Pool 1 are presented in Table 40, respectively, which forms the basis for the ADR information included in the product information, together with clinically relevant abnormal laboratory values which are considered ADRs for mirdametinib.

Table 40: Adverse drug reactions reported for mirdametinib in pool 1

	Paediatric NF1 PN 2 mg/m² BID (N=58)		Adult NF1 PN 2 mg/m² BID (N=75)		Total NF1 PN 2 mg/m² BID (N=133)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Skin and Subcutaneous tissue disorders						
Dermatitis acneiform	25 (43.1%)	1 (1.7%)	62 (82.7%)	5 (6.7%)	87 (65.4%)	6 (4.5%)
Rash[(a)]	19 (32.8%)	1 (1.7%)	13 (17.3%)	1 (1.3%)	32 (24.1%)	2 (1.5%)
Dry Skin	10 (17.2%)	0	10 (13.3%)	0	20 (15.0%)	0
Alopecia	8 (13.8%)	0	9 (12.0%)	0	17 (12.8%)	0
Pruritus	7 (12.1%)	0	10 (13.3%)	0	17 (12.8%)	0
Eczema	8 (13.8%)	0	2 (2.7%)	0	10 (7.5%)	0
Hair colour changes	7 (12.1%)	0	1 (1.3%)	0	8 (6.0%)	0
Hair texture abnormal	3 (5.2%)	0	1 (1.3%)	0	4 (3.0%)	0
Gastrointestinal disorders						
Diarrhoea	31 (53.4%)	3 (5.2%)	41 (54.7%)	0	72 (54.1%)	3 (2.3%)
Nausea	17 (29.3%)	0	41 (54.7%)	0	58 (43.6%)	0
Vomiting	23 (39.7%)	0	28 (37.3%)	0	51 (38.3%)	0
Abdominal pain[(b)]	23 (39.7%)	2 (3.4%)	15 (20.0%)	3 (4.0%)	38 (28.6%)	5 (3.8%)
Constipation	6 (10.3%)	0	14 (18.7%)	0	20 (15.0%)	0
Stomatitis[(c)]	11 (19.0%)	0	4 (5.3%)	0	15 (11.3%)	0
Dry mouth	0	0	5 (6.7%)		5 (6.7%)	
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[d]	24 (41.4%)	1 (1.7%)	31 (41.3%)	5 (6.7%)	55 (41.4%)	6 (4.5%)
General disorders and administration site conditions						
Fatigue	7 (12.1%)	0	27 (36.0%)	1 (1.3%)	34 (25.6%)	1 (0.8%)
Oedema peripheral [e]	3 (5.2%)	0	9 (12.0%)	0	12 (9.0%)	0
Nervous system disorders						
Headache	21 (36.2%)	1 (1.7%)	12 (16.0%)	1 (1.3%)	33 (24.8%)	2 (1.5%)
Investigations						
Decreased ejection fraction	15 (25.9%)	1 (1.7%)	9 (12.0%)	0	2 (18.0%)	1 (0.8%)
Infections and Infestations						

	Paediatric NF1 PN 2 mg/m^2 BID (N=58)		Adult NF1 PN 2 mg/m^2 BID (N=75)		Total NF1 PN 2 mg/m^2 BID (N=133)	
	All Grades (%)	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**	**All Grades (%)**	**Grade ≥3 (%)**
Paronychia	19 (32.8%)	0	2 (2.7%)	0	21 (15.8%)	0
Eye disorders						
Vision blurred	4 (6.9%)	0	7 (9.3%)	0	11 (8.3%)	0
Retinal vein occlusion	0	0	2 (2.7%)	1 (1.3%)	2 (1.5%)	1 (0.8%)
Detachment of retinal pigment epithelium	0	0	1 (1.3%)	0	1 (0.8%)	0
Chemistry						
Increased blood creatine phosphokinase	34 (58.6%)	3 (5.2%)	34 (46.6%)	2 (2.7%)	68 (51.9%)	5 (3.8%)
Increased AST	5 (8.6%)	0	12 (16.4%)	0	17 (13.0%)	0
Increased ALT	12 (20.7%)	0	5 (6.8%)	0	17 (13.0%)	0
Increased Blood alkaline phosphatase	14 (24.1%)	0	10 (13.7%)	0	24 (18.3%)	0
Haematology						
Decreased Neutrophils	17 (29.8%)	6 (10.5%)	6 (8.2%)	1 (1.4%)	23 (17.7%)	7 (5.4%)
Decreased Leukocytes	22 (38.6%)	0	5 (6.8%)	0	27 (20.8%)	0

[(a)] Rash includes Rash, Rash maculo-papular, Rash pustular, Rash erythematous, Rash papular, Exfoliative rash, Papule, Rash macular, Rash pruritic.

[(b)] Abdominal pain includes abdominal pain and abdominal pain upper.

[(c)] Stomatitis includes stomatitis, mouth ulceration, aphthous ulcer.

[d] Musculoskeletal pain includes musculoskeletal pain, myalgia, pain in extremity, back pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, arthralgia, bone pain.

[e] Oedema peripheral includes oedema peripheral, peripheral swelling.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.

Laboratory results are graded according to criteria in NCI-CTCAE version 5.0.

If a participant is missing a result at baseline, the baseline Grade is considered to be Grade 0.

Worsening from baseline is defined as an increase in CTCAE Grade from baseline to worst post-baseline (any CTCAE grade and CTCAE Grade ≥3).

2.6.8.3. Serious adverse event/deaths/other significant events

Serious AEs

Table 41: Incidence of SAEs occurring in participants who received mirdametinib (in descending order of frequency by the total column) - pool 1 - MEK-NF-201 and NF-106

	Pool 1		
	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Number of Participants with at least one SAE	8 (13.8%)	12 (16.0%)	20 (15.0%)
COVID-19	0	2 (2.7%)	2 (1.5%)
Abdominal pain	0	2 (2.7%)	2 (1.5%)
Nephrolithiasis	0	2 (2.7%)	2 (1.5%)
Gastrointestinal viral infection	1 (1.7%)	0	1 (0.8%)
Rotavirus infection	1 (1.7%)	0	1 (0.8%)
Urinary tract infection	0	1 (1.3%)	1 (0.8%)
Colitis ischaemic	0	1 (1.3%)	1 (0.8%)
Fall	1 (1.7%)	0	1 (0.8%)
Femoral neck fracture	1 (1.7%)	0	1 (0.8%)
Near drowning	1 (1.7%)	0	1 (0.8%)
Acute kidney injury	0	1 (1.3%)	1 (0.8%)
Diplopia	1 (1.7%)	0	1 (0.8%)
Retinal vein occlusion	0	1 (1.3%)	1 (0.8%)
Back pain	0	1 (1.3%)	1 (0.8%)
Scoliosis	0	1 (1.3%)	1 (0.8%)
Cerebrovascular accident	0	1 (1.3%)	1 (0.8%)
Seizure	1 (1.7%)	0	1 (0.8%)
Non-cardiac chest pain	1 (1.7%)	0	1 (0.8%)
Dehydration	1 (1.7%)	0	1 (0.8%)
Squamous cell carcinoma of skin	0	1 (1.3%)	1 (0.8%)
Device breakage	1 (1.7%)	0	1 (0.8%)
Chronic obstructive pulmonary disease	0	1 (1.3%)	1 (0.8%)
Pregnancy of partner	0	1 (1.3%)	1 (0.8%)
Hypertension	1 (1.7%)	0	1 (0.8%)

Reference: Table 14.3.3.1.1.
BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; SAE: Serious Adverse event.
All SAEs are coded using MedDRA Version 24.0.
Dose group is based on the assigned dose at baseline.
Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Adverse events of special interest (AESI)

The adverse events of special interest (AESIs) defined in the pivotal study MEK-NF-201 include AEs of Grade ≥3 for the following PTs: diarrhoea, nausea, vomiting, rash, and acneiform rash. AEs of Grade ≥2 for the following PTs were also considered AESIs: RVO, uveitis, optic neuropathy, retinopathy, retinal detachment, ejection fraction decreased, cardiac failure, left ventricular dysfunction, confusion, hallucinations, and delirium.

Table 42: Summary of AESIs by SOC and PT (safety analysis set) in study MEK-NF-201

SOC PT	Paediatric (N = 56)		Adult (N = 58)		Total (N = 114)	
	Participants n (%)	Events	Participants n (%)	Events	Participants n (%)	Events
At Least 1 AESI	19 (33.9%)	26	18 (31.0%)	23	37 (32.5%)	49
Investigations	15 (26.8%)	20	9 (15.5%)	13	24 (21.1%)	33
Ejection fraction decreased	15 (26.8%)	20	9 (15.5%)	13	24 (21.1%)	33
Skin and Subcutaneous Tissue Disorders	2 (3.6%)	2	8 (13.8%)	9	10 (8.8%)	11
Dermatitis acneiform	1 (1.8%)	1	6 (10.3%)	7	7 (6.1%)	8
Rash	1 (1.8%)	1	1 (1.7%)	1	2 (1.8%)	2
Rash erythematous	0	0	1 (1.7%)	1	1 (0.9%)	1
Gastrointestinal Disorders	3 (5.4%)	3	0	0	3 (2.6%)	3
Diarrhoea	3 (5.4%)	3	0	0	3 (2.6%)	3
Eye Disorders	0	0	1 (1.7%)	1	1 (0.9%)	1
Retinal vein occlusion	0	0	1 (1.7%)	1	1 (0.9%)	1
Infections and Infestations	1 (1.8%)	1	0	0	1 (0.9%)	1
Viral rash	1 (1.8%)	1	0	0	1 (0.9%)	1

SOC: system organ class; TEAE: Treatment-Emergent Adverse Event.
All AEs were coded using MedDRA Version 24.0.
N represents the number of participants in the corresponding cohort.
A TEAE was defined as an AE that started or worsened on or after the first dose of study treatment was taken. AEs occurring or increasing in severity up to 30 days after the last dose of study treatment were also classified as treatment-emergent.

Ocular toxicity

In the MEK-NF-201 study, retinal vein occlusion (RVO) was observed in 3% of adult patients, including Grade 3 RVO in 1.7% of patients which resulted in permanent discontinuation. Asymptomatic Grade 1 retinal pigment epithelium detachment (RPED) occurred in 1.7% of patients and was managed without dose modification. Vision blurred was reported by 12% of adult patients. The median time to first onset of ocular toxicity in adults was 147 days. The median time to resolution was 267 days. In these adults, 38% of patients reported resolution of their ocular toxicity, while 25% reported resolution of events with sequelae.

Vision blurred was reported by 7% of paediatric patients. The median time to first onset of vision blurred was 161 days in paediatric patients. The median time to resolution was 29 days. All paediatric patients reported resolution of events of vision blurred.

Decreased left ventricular ejection fraction (LVEF)

In the MEK-NF-201 study, asymptomatic decreased LVEF was reported in 16% of adults. Of these patients, only one reported an LVEF to < 50%, which led to discontinuation followed by return to normal values. Of the remaining adult patients with decreased LVEF, five had a dose interruption, and one patient had a dose reduction. The median time to first onset of decreased LVEF in adults was 70 days. Decreased LVEF resolved in 89% of adult patients. No adult patients had Grade ≥3 events.

In the MEK-NF-201 study, asymptomatic decreased LVEF was reported in 27% of paediatric patients. Of these patients, one reported an LVEF to < 50%, which returned to normal values without dose modification. One patient had a Grade 3 decreased LVEF that resolved without dose modification and another patient with Grade 2 decreased LVEF had a dose interruption. The remaining 12 patients' events of decreased LVEF were Grade 2 and no action was taken with study treatment in response to

any of these events. The median time to first onset of decreased LVEF in paediatric patients was 132 days. Decreased LVEF resolved in 67% of paediatric patients.

Skin toxicity

In the MEK-NF-201 study, dermatitis acneiform and non-acneiform rashes occurred in 90% of adult patients. Grade 3 dermatitis acneiform and other rashes occurred in 9% and 1.7% of adult patients, respectively. Rashes resulted in discontinuations in 10% of adults and dose reductions in 10% of adults. The median time to first onset of rashes was 9 days in adult patients. The median time to resolution was 115 days. In these adult patients, 33 (64%) reported resolution of their rashes, 3 (6%) reported resolution with sequelae, and 8 (15%) reported that their rashes were resolving.

In the MEK-NF-201 study, dermatitis acneiform and non-acneiform rashes occurred in 70% of paediatric patients. Grade 3 dermatitis acneiform and non-acneiform rashes occurred in 1.8% and 1.8%, respectively. Rashes resulted in discontinuations in 4% of paediatric patients, and dose reductions in 4% of paediatric patients. Dermatitis acneiform occurred with a higher frequency in patients aged 12 to 17 years, while other rashes occurred with a higher frequency in patients aged 2 to 11 years. The median time to first onset of rashes in paediatric patients was 15 days. The median time to resolution was 155 days. In these paediatric patients, 27 (69%) reported resolution of their rashes and 3 (8%) reported that their rashes were resolving.

Musculoskeletal pain

In the MEK-NF-201 study, musculoskeletal pain (including musculoskeletal pain, myalgia, pain in extremity, back pain, musculoskeletal chest pain, neck pain, non-cardiac chest pain, arthralgia, and bone pain) were reported by 41% of adult and 41% of paediatric patients. Concomitant medications used to treat musculoskeletal pain included non-steroidal anti-inflammatory medicinal products, non-opioid analgesics and glucocorticoids. Musculoskeletal pain should be treated as clinically indicated.

AST and ALT increased

In the MEK-NF-201 study, laboratory shifts of ALT increased were observed in 9% of adult and 21% of paediatric patients. Laboratory shifts of AST increased were observed in 18% of adult and 9% of paediatric patients. All events were mild to moderate severity with no Grade 3 events reported. ALT and AST increased did not result in any discontinuations, dose reductions or interruptions. Increases in ALT and AST should be monitored and managed as clinically indicated.

Deaths

One death occurred in the pool 1 and came from the study MEK-NF-201. There was no death in the paediatric cohort. The death was in the adult cohort and was considered by the investigator to be unrelated to study treatment but rather due to COVID-19.

2.6.8.4. Laboratory findings

Table 43: Selected laboratory abnormalities worsening from baseline - Pool 1 - MEK-NF-201 and NF-106

	Pediatric NF1 PN 2 mg/m² BID (N=58)		Adult NF1 PN 2 mg/m² BID (N=75)		Total NF1 PN 2 mg/m² BID (N=133)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Chemistry						
Increased blood creatine phosphokinase	34 (58.6%)	3 (5.2%)	34 (45.3%)	2 (2.7%)	68 (51.1%)	5 (3.8%)
Increased AST	5 (8.6%)	0	12 (16.0%)	0	17 (12.8%)	0
Increased ALT	12 (20.7%)	0	5 (6.7%)	0	17 (12.8%)	0
Increased Blood alkaline phosphatase	16 (27.6%)	0	10 (13.3%)	0	26 (19.5%)	0
Hematology						
Decreased Neutrophils	17 (29.3%)	6 (10.3%)	6 (8.0%)	1 (1.3%)	23 (17.3%)	7 (5.3%)
Echocardiography						
Decreased ejection fraction	15 (25.9%)	1 (1.7%)	10 (13.3%)	0	25 (18.8%)	1 (0.8%)

Reference: Table 14.4.6.1.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.
Laboratory results are graded according to criteria in NCI-CTCAE version 5.0.
If a participant is missing a result at baseline, the baseline Grade is considered to be Grade 0.
Worsening from baseline is defined as an increase in CTCAE Grade from baseline to worst post-baseline (any CTCAE grade and CTCAE Grade ≥3).

Urinalysis

None of the studies except the study MEK-NF-201 collected urinalysis data. No clinically relevant changes in urinalysis parameters were observed in either cohort.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 44: TEAEs with age-associated trends in participants who received mirdametinib - pool 1 - MEK-NF-201 and NF-106

	Pool 1						
	Pediatric NF1 PN 2 mg/m² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m² BID Age 12-<18 years (N=26)	Pediatric NF1 PN 2 mg/m² BID Total (N=58)	Adult NF1 PN 2 mg/m² BID Age 18-<40 (N=57)	Adult NF1 PN 2 mg/m² BID Age 40-<65 (N=16)	Adult NF1 PN 2 mg/m² BID Age ≥65 (N=2)	Adult NF1 PN 2 mg/m² BID Total (N=75)
TEAEs where incidence increases with decreasing age							
Abdominal pain	10 (31.3%)	6 (23.1%)	16 (27.6%)	8 (14.0%)	3 (18.8%)	1 (50.0%)	12 (16.0%)
Abdominal pain upper	6 (18.8%)	3 (11.5%)	9 (15.5%)	0	3 (18.8%)	0	3 (4.0%)
Blood creatine phosphokinase increased	8 (25.0%)	6 (23.1%)	14 (24.1%)	9 (15.8%)	1 (6.3%)	1 (50.0%)	11 (14.7%)
Cough	10 (31.3%)	3 (11.5%)	13 (22.4%)	4 (7.0%)	1 (6.3%)	1 (50.0%)	6 (8.0%)
Eczema	7 (21.9%)	1 (3.8%)	8 (13.8%)	2 (3.5%)	0	0	2 (2.7%)
Ejection fraction decreased	9 (28.1%)	6 (23.1%)	15 (25.9%)	4 (7.0%)	4 (25.0%)	1 (50.0%)	9 (12.0%)
Hair colour changes	6 (18.8%)	1 (3.8%)	7 (12.1%)	1 (1.8%)	0	0	1 (1.3%)
Headache	13 (40.6%)	8 (30.8%)	21 (36.2%)	9 (15.8%)	2 (12.5%)	1 (50.0%)	12 (16.0%)
Nasal congestion	5 (15.6%)	3 (11.5%)	8 (13.8%)	4 (7.0%)	0	0	4 (5.3%)
Neutrophil count decreased	4 (12.5%)	3 (11.5%)	7 (12.1%)	0	0	0	0
Oropharyngeal pain	4 (12.5%)	2 (7.7%)	6 (10.3%)	1 (1.8%)	0	0	1 (1.3%)
Paronychia	11 (34.4%)	8 (30.8%)	19 (32.8%)	2 (3.5%)	0	0	2 (2.7%)
Pharyngitis streptococcal	6 (18.8%)	0	6 (10.3%)	0	0	0	0
Pyrexia	10 (31.3%)	1 (3.8%)	11 (19.0%)	2 (3.5%)	2 (12.5%)	0	4 (5.3%)
Rash	9 (28.1%)	2 (7.7%)	11 (19.0%)	3 (5.3%)	1 (6.3%)	0	4 (5.3%)
Rhinitis allergic	6 (18.8%)	0	6 (10.3%)	0	0	0	0
Stomatitis	7 (21.9%)	1 (3.8%)	8 (13.8%)	3 (5.3%)	0	0	3 (4.0%)
Upper respiratory tract infection	10 (31.3%)	5 (19.2%)	15 (25.9%)	1 (1.8%)	0	0	1 (1.3%)
Weight increased	4 (12.5%)	5 (19.2%)	9 (15.5%)	6 (10.5%)	1 (6.3%)	0	7 (9.3%)
White blood cell count decreased	3 (9.4%)	3 (11.5%)	6 (10.3%)	1 (1.8%)	0	0	1 (1.3%)

No particular safety issues have been identified from data with respect to age, sex, race, ethnicity, BMI, in the NF1 PN population.

No dedicated studies have been performed in patients with hepatic, renal or cardiac impairment.

Overdose, drug abuse, withdrawal and rebound: there were no data on drug abuse, withdrawal and rebound that allow any causal relationship with mirdametinib to be established. No specific information on overdose with mirdametinib is available.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Safety data related to DDI are detailed under section 2.6.2.1. Pharmacokinetics, sub-section PK interactions studies and 2.6.2.2. Pharmacodynamics.

2.6.8.9. Discontinuation due to adverse events

Table 45: Incidence of TEAEs leading to treatment discontinuation in participants who received mirdametinib (in descending order of frequency by the total column) - pool 1 - MEK-NF-201 and NF-106

Preferred Term	Pool 1		
	Paediatric NF1 PN 2mg/m² BID	Adult NF1 PN 2mg/m² BID	Total NF1 PN 2mg/m² BID
	(N=58)	(N=75)	(N=133)
Number of Participants with at least one TEAE leading to Study Treatment Discontinuation	5 (8.6%)	16 (21.3%)	21 (15.8%)
Dermatitis acneiform	1 (1.7%)	6 (8.0%)[a],[b],[c]	7 (5.3%)
Diarrhoea	1 (1.7%)[d]	4 (5.3%)	5 (3.8%)
Nausea	0	4 (5.3%)	4 (3.0%)
Rash	1 (1.7%)	1 (1.3%)	2 (1.5%)
Urticaria	2 (3.4%)	0	2 (1.5%)
Abdominal pain	1 (1.7%)	1 (1.3%)	2 (1.5%)
Vomiting	0	2 (2.7%)	2 (1.5%)
Alopecia	0	1 (1.3%)	1 (0.8%)
Dry skin	0	1 (1.3%)[e]	1 (0.8%)
Rash erythematous	0	1 (1.3%)	1 (0.8%)
Constipation	1 (1.7%)	0	1 (0.8%)
Dizziness	0	1 (1.3%)	1 (0.8%)
Headache	0	1 (1.3%)	1 (0.8%)
Paraesthesia	0	1 (1.3%)	1 (0.8%)
Retinal vein occlusion	0	1 (1.3%)	1 (0.8%)
Peripheral swelling	0	1 (1.3%)	1 (0.8%)
COVID-19	0	1 (1.3%)	1 (0.8%)
Ejection fraction decreased	0	1 (1.3%)	1 (0.8%)
Cough	0	1 (1.3%)	1 (0.8%)
Wheezing	0	1 (1.3%)	1 (0.8%)

AE: Adverse event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.

All TEAEs are coded using MedDRA Version 24.0.

Dose group is based on the assigned dose at baseline.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

· TEAES leading to interruptions or dose modifications

Table 46: TEAEs leading to treatment interruption and dose modifications – pool 1 - MEK-NF-201 and NF-106

	Pool 1		
	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Duration of Mirdametinib Exposure (Months)			
N	58	75	133
Mean (StD)	20.86 (10.690)	18.04 (13.002)	19.27 (12.087)
Median	21.87	18.66	21.85
Min, Max	1.6, 40.1	0.4, 45.6	0.4, 45.6
Total Duration of Exposure (years) for all Participants	100.8	112.7	213.5
Number of Participants who Received Study Treatment			
For at least 1 month	58 (100%)	70 (93.3%)	128 (96.2%)
For at least 2 months	57 (98.3%)	68 (90.7%)	125 (94.0%)
For at least 3 months	56 (96.6%)	68 (90.7%)	124 (93.2%)
For at least 6 months	51 (87.9%)	60 (80.0%)	111 (83.5%)
For at least 12 months	42 (72.4%)	41 (54.7%)	83 (62.4%)
For at least 24 months	24 (41.4%)	26 (34.7%)	50 (37.6%)
For at least 36 months	6 (10.3%)	10 (13.3%)	16 (12.0%)
Number of Participants Receiving All Planned Doses	18 (31.0%)	27 (36.0%)	45 (33.8%)
Participants With at least 1 Dose Modification	40 (69.0%)	48 (64.0%)	88 (66.2%)

	Pool 1		
	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Time to Dose Modification (Months)			
n	40	48	88
Mean (StD)	7.37 (6.673)	5.96 (8.939)	6.60 (7.977)
Median	4.24	1.37	3.57
Min, Max	0.0, 21.6	0.0, 44.8	0.0, 44.8
Participants With at least 1 Dose Reduction due to a TEAE	7 (12.1%)	15 (20.0%)	22 (16.5%)
Time to Dose Reduction (Months)			
n	7	9	16
Mean (StD)	3.45 (4.734)	5.09 (6.319)	4.37 (5.565)
Median	1.74	1.22	1.48
Min, Max	0.3, 13.9	0.3, 14.4	0.3, 14.4
Participants With at least 1 Dose Interruption	17 (29.3%)	21 (28.0%)	38 (28.6%)
Interruption Due to a TEAE	17 (100%)	21 (100%)	38 (100%)
TEAE Related to Study Treatment	8 (47.1%)	7 (33.3%)	15 (39.5%)

Table 47: Incidence TEAEs leading to dose interruption in participants who received mirdametinib (in descending order of frequency by the total column; pool 1 - MEK-NF-201 and NF-106)

Preferred Term	Pool 1		
	Paediatric NF1 PN 2mg/m² BID	Adult NF1 PN 2mg/m² BID	Total NF1 PN 2mg/m² BID
	(N=58)	(N=75)	(N=133)
Number of Participants with at least one TEAE leading to Dose Interruption	17 (29.3%)	21 (28.0%)	38 (28.6%)
Ejection fraction decreased	1 (1.7%)	5 (6.7%)	6 (4.5%)
COVID-19	3 (5.2%)	3 (4.0%)	6 (4.5%)
SARS-CoV-2 test positive	3 (5.2%)	1 (1.3%)	4 (3.0%)
Neutrophil count decreased	2 (3.4%)	0	2 (1.5%)
Dermatitis acneiform	0	2 (2.7%)	2 (1.5%)
Blood creatine phosphokinase increased	1 (1.7%)	0	1 (0.8%)
Weight increased	1 (1.7%)	0	1 (0.8%)

Preferred Term	Pool 1		
	Paediatric NF1 PN 2mg/m² BID	Adult NF1 PN 2mg/m² BID	Total NF1 PN 2mg/m² BID
	(N=58)	(N=75)	(N=133)
Cellulitis	0	1 (1.3%)	1 (0.8%)
Gastrointestinal infection	1 (1.7%)	0	1 (0.8%)
Kidney infection	0	1 (1.3%)	1 (0.8%)
Rash pustular	0	1 (1.3%)	1 (0.8%)
Rotavirus infection	1 (1.7%)	0	1 (0.8%)
Viral rash	1 (1.7%)	0	1 (0.8%)
Abdominal pain	1 (1.7%)	0	1 (0.8%)
Colitis ischaemic	0	1 (1.3%)	1 (0.8%)
Dental caries	1 (1.7%)	0	1 (0.8%)
Diarrhoea	1 (1.7%)	0	1 (0.8%)
Oral pain	1 (1.7%)	0	1 (0.8%)
Stomatitis	0	1 (1.3%)	1 (0.8%)
Vomiting	0	1 (1.3%)	1 (0.8%)
Buttock injury	1 (1.7%)	0	1 (0.8%)
Fall	1 (1.7%)	0	1 (0.8%)
Near drowning	1 (1.7%)	0	1 (0.8%)
Procedural pain	1 (1.7%)	0	1 (0.8%)
Skin ulcer	0	1 (1.3%)	1 (0.8%)
Urticaria	1 (1.7%)	0	1 (0.8%)
Cerebrovascular accident	0	1 (1.3%)	1 (0.8%)
Seizure	1 (1.7%)	0	1 (0.8%)
Syncope	0	1 (1.3%)	1 (0.8%)
Chronic obstructive pulmonary disease	0	1 (1.3%)	1 (0.8%)
Laryngeal oedema	1 (1.7%)	0	1 (0.8%)
Oropharyngeal pain	1 (1.7%)	0	1 (0.8%)
Ocular discomfort	0	1 (1.3%)	1 (0.8%)
Vision blurred	0	1 (1.3%)	1 (0.8%)
Acute kidney injury	0	1 (1.3%)	1 (0.8%)
Nephrolithiasis	0	1 (1.3%)	1 (0.8%)
Neutropenia	1 (1.7%)	0	1 (0.8%)
Influenza like illness	0	1 (1.3%)	1 (0.8%)
Soft tissue disorder	0	1 (1.3%)	1 (0.8%)

Preferred Term	Pool 1		
	Paediatric NF1 PN 2mg/m² BID	Adult NF1 PN 2mg/m² BID	Total NF1 PN 2mg/m² BID
	(N=58)	(N=75)	(N=133)
Device breakage	1 (1.7%)	0	1 (0.8%)

AE: Adverse event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.
All TEAEs are coded using MedDRA Version 24.0.
Dose group is based on the assigned dose at baseline.
Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.
Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

2.6.8.10. Post marketing experience

Mirdametinib was approved on 11 February 2025, by the US Food and Drug Administration for the treatment of adult and paediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection. There is no relevant post marketing safety information available yet.

2.6.9. Discussion on clinical safety

The safety profile of mirdametinib is based on the pivotal study MEK-NF-201, and on a phase 2 investigator-initiated study, NF-106. The safety data from both studies were analysed together as a single pool (also called pool 1) and are the primary safety data used to assess the safety profile of mirdametinib in adult and paediatric participants with NF1 PN.

In the paediatric cohort of the pool 1, a total of 58 participants were exposed to at least 1 dose of mirdametinib and had a similar median duration of exposure, 21.87 months to that in study MEK-NF-201, 22 months. A total of 72% of participants in the paediatric cohort were on study treatment for 1 year or longer, 41% for 2 years or longer and 10% for 3 years or longer with the primary reason for discontinuation from study treatment being progression of disease.

In the adult cohort of the pool 1, a total of 75 participants were exposed to at least 1 dose of mirdametinib. 55% of all participants were on study treatment for 1 year or longer, 35% for 2 years or longer and 13% for 3 years or longer with the primary reason for discontinuation from study treatment due to an adverse event.

As nearly one year had passed between the DCO of MEK-NF-201 (20 September 2023) and the submission of this MAA (July 2024), the applicant provided an update on the safety profile of mirdametinib during this period (data not shown). No new safety issues were identified.

Adverse events

All patients experienced at least one adverse event in the pool 1, and in 97% total of patients, these AEs were considered as related to the studied treatment. Almost all patients experienced AEs of interest, more in the adult cohort than in the paediatric cohort. One-third of patients experienced grade 3 or more TEAEs.

TEAEs - Treatment emergent adverse events

In the pool 1, the most commonly reported AEs were under the SOC "Skin and Subcutaneous Tissue Disorders" followed by "Gastrointestinal Disorders" and "Infections and Infestations".

The frequency of TEAEs in the pool 1 was not always similar between the paediatric and the adult cohorts. Frequently occurring (≥15%) TEAEs of headache, abdominal pain, COVID-19, blood creatine phosphokinase increased, ejection fraction decreased, paronychia, cough, upper respiratory tract infection, weight increased, rash, pyrexia and abdominal pain upper occurred at a higher frequency in the paediatric cohort than in the adult cohort.

In respect to the adverse events by time to onset, most patients in the pool 1 reported their first TEAE during cycle 1 (90% total; 79% paediatric, 97% adult) and the first onset of most TEAEs either decreased after cycle 1 or remained relatively stable throughout the duration of treatment.

Just over a third of patients experienced at least one grade 3 or above TEAEs, the most frequently reported grade ≥3 TEAEs (≥4%) were dermatitis acneiform (5%), blood creatine phosphokinase increased (4%), neutrophil count decreased (4%), and abdominal pain (4%).

Treatment related adverse events

The incidence of treatment-related AEs was generally similar in both the paediatric and adult cohorts.

The following treatment-related AEs were reported in ≥10% of paediatric patients and also were reported at a greater incidence (>1.5x) than the adult patients: rash (12% vs 5%), eczema (10% vs 3%), hair colour changes (10% vs 1%), abdominal pain (14% vs 7%), abdominal pain upper (10% vs 3%), blood creatine phosphokinase increased (22% vs 12%), ejection fraction decreased (19% vs 9%), weight increased (14% vs 4%), paronychia (31% vs 3%), and headache (10% vs 4%). Neutrophil count decreased and hypertriglyceridemia were reported in 9% and 7% of paediatric patients, respectively, and 0% of adult patients.

The following treatment-related AEs were reported in ≥10% of adult patients and also were reported at a greater incidence (>1.5x) than the paediatric patients: dermatitis acneiform (83% vs 43%), nausea (41% vs 22%), vomiting (28% vs 14%), constipation (11% vs 5%), pruritus (11% vs 5%), fatigue (29% vs 9%), and dizziness (12% vs 3%).

Grade ≥3 treatment-related AEs were reported in 19% of patients in the pool 1. The most frequently reported treatment-related Grade ≥3 AEs (≥4%) were dermatitis acneiform (5%), blood creatine phosphokinase increased (4%), and neutrophil count decreased (4%). Treatment-related Grade ≥3 TEAEs reported by ≥2 paediatric patients were neutrophil count decreased, blood creatine phosphokinase increased, weight increased, and abdominal pain. Dermatitis acneiform was the only treatment-related Grade ≥3 TEAE reported by ≥2 adult patients.

ADRs - Adverse drug reactions

ADRs for mirdametinib were defined as those AEs considered related to mirdametinib based on the assessment of numerical frequency data and review of individual case details such as temporal association of the event with administration of mirdametinib, dechallenge and rechallenge information, and confounding factors such as intercurrent illnesses and administration of concomitant medications which could be plausible alternative causes for the reported events. The ADR table along with their frequencies has been included in section 4.8 of the SmPC.

Serious adverse events

The incidence of serious adverse events in the pool 1 was quite similar in both paediatric (8 patients [13.8%]) and adult cohorts (12 patients [16%]), and patients with at least one SAE was 20 (15%). Most of these events (18 (16%) were reported in the study MEK-NF-201: 8 (14%) in paediatric patients and 10 (17%) in adult patients, corresponding to 11 and 13 events, respectively. No SAE was considered related to mirdametinib in the paediatric cohort. Nevertheless, from the narratives, 2 SAE of ejection fraction decreased occurred in two paediatric patients and the applicant has assessed the events as related to mirdametinib and are further discussed in the section below (AESIs)

In the paediatric group, the other reported SAE, not related to mirdametinib, were femoral neck fracture (n=1), gastrointestinal viral infection (n=1), rotavirus infection (n=1), non-cardiac chest pain (n=1), diplopia, (n=1), dehydration (n=1), fall (n=1), worsening hypertension (n=1), seizure (n=1).

In adult patients, none of the following SAEs were related to mirdametinib: chronic obstructive pulmonary disease (n=1), scoliosis (n=1), diarrhoea (n=1), acute kidney injury (n=1), abdominal pain (n=1), squamous cell carcinoma (n=1), stroke (n=1), colitis ischemic (n=1), nephrolithiasis (1).

For one adult (1 event), the SAE of retinal vein occlusion (RVO) event was considered as related to mirdametinib by the applicant. The patient had no history nor evidence of retinal pathology on previous retinal examination, had normal baseline ophthalmology examination with normal optical coherence tomography and fundus autofluorescence, and normal ophthalmological examination during the protocol-directed Cycle 5 Day 15 assessment; pupil dilation was not conducted for the Cycle 5 Day 15 assessment.

In the study NF-106, 2 adult patients reported 7 serious adverse events: abdominal pain (n=3), back pain (n= 2 events) and pregnancy of partner (n= 2 events in the listing whilst the event occurred in one patient). One of these two patients experienced 5 events (abdominal pain and pack pain) considered related to mirdametinib. Of note, the reason of the pregnancy was "*noncompliance with contraception fathered the pregnancy*". No paediatric patient had a serious AE in this study.

AESIs - Adverse events of special interest

- Eye disorders: The events pertained to the risk of ocular hypertension, corneal effects, retinal effects as retinal vein occlusion (RVO), retinopathy, optic neuropathy, conjunctival and eyelid disorders, and diplopia. Regarding RVO, the safety data are sufficiently relevant to consider at least a reasonable possibility for a causal association with mirdametinib and this adverse drug reaction is listed under section 4.8 of the SmPC and PL. Moreover, the safety specifications of the RMP mention this risk as an important identified risk which is supported. Except for RVO, the causal association between other events and mirdametinib is difficult to establish. It is also agreed that the available data do not support increased IOP (intraocular pression), and corneal effects, as a risk with mirdametinib.

Retinal pigment epithelial detachment (RPED) was identified in one adult patient and, according to the provided line-listing on adverse events in study MEK-NF-201, this event has been included as related to mirdametinib. None of the events was reported in paediatric patients. Additionally, no serious event was reported from mirdametinib compassionate use programme. Furthermore, literature data proposed a possible mechanism behind MEK-inhibitor associated retinopathy, as RPED. These data are sufficiently relevant to consider a causal association at least as a reasonable possibility with mirdametinib and RPED wase added in the list of ADRs of the section 4.8 and in the PL and as an important identified risk in the RMP.

Ocular events (RVO, RPED, vision blurred) will be further investigated through the PASS (see section below 'Additional safety data needed in the context of a conditional MA').

Patients should be advised to report any new visual disturbances. RVO (retinal vein occlusion) and RPED (retinal pigment epithelial detachment) were commonly reported in adult patients receiving Ezmekly in clinical studies. A comprehensive ophthalmological evaluation should be performed prior to treatment initiation, at regular intervals during treatment, and at any time a patient reports new or worsening visual changes. For ocular adverse reactions, mirdametinib therapy should be interrupted and then dose reduced or treatment permanently discontinued based on severity of the adverse reaction. If RVO is diagnosed, treatment with mirdametinib should be permanently discontinued. If symptomatic RPED is diagnosed, treatment with mirdametinib should be interrupted until resolution and the dose reduced when treatment is resumed. In patients diagnosed with RPED without reduced visual acuity, treatment can be continued but ophthalmic assessment should be conducted every 3 weeks until resolution (see sections 4.2, 4.4 and 4.8 of the SmPC).

- Left ejection fraction decreased (LEFD) events:

Asymptomatic decrease in LVEF ≥ 10% from baseline occurred in 17% of adult patients and 27% of paediatric patients in the ReNeu study. All cases of decreased LVEF in adult or paediatric patients in the clinical studies were asymptomatic.

Based on these data, and the biological plausibility for MEK inhibition to play a role in the event, and other drugs within the same class having similar effects, ejection fraction decreased is listed as an ADR under section 4.8 of the SmPC and also in the list of the RMP safety concerns as an important identified risk.

Patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional lower limit of normal (LLN) have not been studied. LVEF should be evaluated by echocardiogram before initiation of treatment to establish baseline values, every 3 months during the first year, then as clinically indicated thereafter. Prior to starting treatment, patients should have an ejection fraction above the institutional LLN. Decreased LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation (see sections 4.2, 4.4 and 4.8 of the SmPC).

Ejection fraction decreased will be further investigated through the PASS (see section below 'Additional safety data needed in the context of a conditional MA').

- Skin disorders: The safety data analysed in patients from studies MEK-NF-201 and NEF-106 support skin disorders such as dermatitis acne, dry skin, rash, pruritus, paronychia, hair changes as to be related to mirdametinib. No serious cutaneous adverse reactions have been reported. Therefore, these events are reflected as ADR in section 4.8 of the SmPC. These skin disorders have been added in the RMP under section on risks not considered important for inclusion in the list of safety concerns. These proposals are endorsed.

Patients should contact their doctor or nurse if they experience any skin reactions. Supportive care, e.g. the use of emollient creams, should be initiated at first signs of skin toxicity. Mirdametinib therapy should be interrupted, the dose reduced or permanently discontinued based on severity of the adverse reaction (see sections 4.2, 4.4 and 4.8 of the SmPC).

- Gastrointestinal disorders: the safety data from studies MEK-NF-201 and NEF-106 support diarrhoea, nausea, vomiting, abdominal pain, and constipation as related to mirdametinib. Therefore, these events are listed as ADRs in section 4.8 of the SmPC. Likewise, these gastrointestinal adverse events have been added in the RMP under the section on risks not considered important for inclusion in the list of safety concerns. These proposals are endorsed.

- Neutrophil count decreased: Neutrophil count decreased have been reported in 7 paediatric patients and no adult patients. Based on the incidence of neutrophil count decreased, notably in paediatric NF1 PN population, the biological plausibility for MEK inhibition to play a role in the event, the data support

a reasonable causal association with mirdametinib treatment and has therefore been listed as an ADR in section 4.8 of the SmPC. Furthermore, no opportunistic infection or serious events of neutrophil count decreased were reported therefore this ADR was added in the RMP under section on risks not considered important for inclusion in the list of safety concerns in the RMP.

- Haemoglobin decreased: Adverse events related to haemoglobin decreased were reported, mainly anaemia. Seventeen (17) events of anaemia occurred in 7 patients: 1 paediatric and 3 adult patients in the study MEK-NF-201. For most of the cases, the event was considered related to the study treatment however, since no action was taken towards mirdametinib, and the patients recovered, a conclusion on mirdametinib causal association cannot be presently made and the event is not added to section 4.8 of the SmPC.

- Lymphocyte count decreased were observed in both 5 patients (2 paediatrics and 3 adults). One paediatric patient experienced the AE of lymphocytes count increased. No causal association with mirdametinib can be made from these AEs and the event is not added to section 4.8 of the SmPC.

- Central nervous system adverse events were reported in 62 (47%) patients in the pool 1, mostly headache, dizziness and paraesthesia.

The available data do not allow to establish a causal relationship between mirdametinib and dizziness or paraesthesia. However, several patients in both studies experienced headache under mirdametinib treatment that was considered related to the study treatment, no action was taken towards mirdametinib, the patients did not always recover and when they did, this was due to the use of an antalgic drug. A causal relationship with mirdametinib is suspected. The adverse event of "headache" has been added in the list of ADR in section 4.8 of the SmPC.

- The appraisal of the adverse events of fatigue and blood creatinine phosphokinase increased lead to conclude that available data are sufficiently relevant to consider a reasonable causality with mirdametinib. Therefore, both events have been listed in section 4.8 of the SmPC. This is endorsed.

- Bone effects: Based on the non-clinical data which provides evidence on the risk of multifocal dysplasia in epiphyseal growth plate and although the reported cases did not allow any causal association to be made with mirdametinib, the limited data on long-term exposure doesn't allow to capture any related signal. The risk of physeal dysplasia was added to the list of safety concerns as an important potential risk in the RMP. The long-term safety data will allow to better assess the impact of mirdametinib on bone effects notably in paediatric patients.

- Weight increased: 13 patients experienced an adverse event of weight increased, for 11 patients, the event was related to mirdametinib. Three patients experienced grade 3 weight increased. Based on available data, it is not possible to establish a possible causal association between mirdametinib and weight increased. In paediatric patients, the data are biased by the natural growth and., In adult patients, most had also an underlying disease of depression treated with antidepressant drugs (e.g. sertraline) that could have also contributed to the weight increased.

- As regards the AESI of thromboembolic events, renal effects, cough, upper respiratory tract infection, opportunistic infections, hypersensitivity and muscle effects (myalgia, myositis, muscle weakness), the provided data does not allow to establish acausal association with mirdametinib. Patients are confounded either by their underlying disease or their medical history. These adverse events will be monitored by routine pharmacovigilance activities.

Deaths

One death occurred in the pool 1 from study MEK-NF-201 in the adult cohort and was considered by the investigator to be unrelated to study treatment but rather due to COVID-19.

There were no deaths in the paediatric cohort.

Laboratory and other findings

See also haematology and biochemistry parameters discussed previously under AESIs.

Platelet count decreased: In study MEK-NF-201, one paediatric patient experienced platelet count decreased related to the study treatment, not action was taken and the outcome of the patient is unknown. Six adverse events of platelet count decreased have been reported in study NF-106. It is agreed that available data cannot allow any causal association between mirdametinib and the adverse event of platelet count decreased to be established. Patients who experienced this AE resolved under study treatment without changes.

Electrocardiogram**:** Safety issues on TQT effects are discussed in the section "Clinical Pharmacology" of this report.

Safety in special populations

Pregnancy and lactation: there are limited clinical data available on the use of mirdametinib in pregnant women. There was one case of pregnancy in study MEK-NF-201 for which the outcome is unknown. Due to the observations in animal studies (see Non-clinical section of this report) and the limited information concerning the use of mirdametinib in pregnant women, use of mirdametinib is not recommended during pregnancy and in women of childbearing potential not using contraception.

The effects on the ability to drive or operate machinery or impairment of mental ability have not been formally studied with mirdametinib. However, the analyses of treatment related adverse events that may alter the vigilance of the patients identified fatigue and blurred vision as a consequence, Ezmekly may have a moderate influence on the ability to drive and use machines. Patients who experience these symptoms should observe caution when driving or using machines (a warning has been included in section 4.7 of the SmPC).

Discontinuation or interruption due to adverse events

About 15.8% (n=21) of all patients in the pool 1 discontinued study treatment due to TEAEs, including 8.6% (n=5) of patients in the paediatric cohort and 21.3% (n=16) of patients in the adult cohort.

In the paediatric cohort, the only TEAE that led to treatment discontinuation in more than 1 patient was urticaria which resulted in treatment discontinuation in 2 (3%) paediatric patients (both come from the study MEK-NF-201). All TEAEs that led to treatment discontinuation were grade 1 or grade 2.

In the adult cohort, TEAEs that led to discontinuation in more than 1 patient were dermatitis acneiform [6 (8%) patients], diarrhoea and nausea [4 (5%) patients each], and vomiting [2 (3%) patients]. Most were grade 1 or 2 but 3 TEAEs were grade 3 (dermatitis acneiform, rash erythematous, and RVO), no grade 4 TEAEs were reported and 1 TEAE was grade 5 (COVID-19)".

Interruption due to adverse events

In the pool 1, 38 (28.6%) patients presented at least 1 dose interruption due TEAEs: 17 (29.3%) paediatric patients and 21 (28%) adult patients. Eight (47.1%) paediatric and seven (33.3%) adult patients interrupted due to TEAE related to mirdametinib with a median of time to dose interruption of 6 months. Twenty-two (16.5%) patients had at least 1 dose reduction due to a TEAE: 7 (12.1%) paediatric patients and 15 (20.0%) adult patients.

Other safety issues

Safety data linked to long-term use of mirdametinib in both adult and paediatric patients appears to be limited. The applicant has committed to conduct and submit the results of a non-interventional post-authorisation safety study (PASS); see section below.

Additional safety data needed in the context of a conditional MA

In order to confirm that the safety profile of mirdametinib is acceptable over long term use, the applicant has committed to conduct and submit the results of a non-interventional PASS as part of the specific obligations to be fulfilled in the context of this CMA (**SOB**). This PASS will be a multiple-country prospective cohort study, which primary objective will be to estimate the incidence of physeal dysplasia in patients aged 2 to < 18 years treated with mirdametinib for up to 6 years, and to further characterise the long-term safety in both adult and paediatric patients aged 2 years and above. Other safety concerns that will be addressed with the PASS: ocular events (RVO, RPED, vision blurred), ejection fraction decreased, adverse effects on cardiac conduction, embryo-foetal toxicity and carcinogenicity.

2.6.10. Conclusions on the clinical safety

All patients from both cohorts, paediatric and adult, experienced several adverse events, however, the toxicity is mild or moderate in severity and was managed by dose adjustments reductions, namely interruptions, discontinuations respectively in paediatric and adult patients. These indicate that tolerability of mirdametinib is impacted but remains manageable, with treatment discontinuation in 7% of paediatric and 20% of adult patients.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

Non-interventional post-authorisation safety study (PASS): In order to confirm the long-term safety of mirdametinib, in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should conduct and submit the results of a study conducted in patients with NF1 who have been prescribed at least one dose of mirdametinib and who are aged 2 and above at the start of mirdametinib.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 48: Summary of safety concerns

Summary of Safety Concerns	
Important identified risks	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased
Important potential risks	Embryo-foetal toxicity Physeal dysplasia Adverse effects on cardiac conduction Carcinogenicity
Missing information	Long term safety

2.7.2. Pharmacovigilance plan

Table 49: Summary table of additional pharmacovigilance activities

On-going and planned additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)*				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				
Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study	Primary objectives: To estimate the incidence of physeal dysplasia in patients aged 2 to < 18 years (paediatric cohort) with NF1 for the treatment of symptomatic PNs, and long term safety based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years. To further characterise the long-term safety in both adult and paediatric patients aged 2 years and above (adult and paediatric cohort) for the treatment of symptomatic PNs based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years.	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased Adverse effects on cardiac conduction Embryo-foetal toxicity Physeal dysplasia in paediatric patients Carcinogenicity Long term safety	Submission for Scientific Advice to SAWP/PRAC Submission of full protocol to PRAC Progress reports Final study report	July 2025 Approximately 5 months following EC decision Annually following start of data collection August 2033
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
None				

2.7.3. Risk minimisation measures

Table 50: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Ocular events (RVO, RPED, Vision blurred) (Important Identified Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. PIL • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects EZMEKLY.	
	Additional risk minimisation measures: None	<u>Additional pharmacovigilance activities:</u> Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Ejection Fraction Decreased (Important Identified Risk)	**Routine risk minimisation measures:** <u>Routine risk communication</u>: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. <u>Routine risk minimisation activities recommending specific clinical measures to address the risk</u>: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. PIL	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	• Section 2: What you need to know before you take EZMEKLY.	
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Embryo-Foetal Toxicity (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy, and lactation. • Section 5.3: Preclinical safety data. PIL • Section 2: What you need to know before you take EZMEKLY. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy, and lactation. PIL • Section 2: What you need to know before you take EZMEKLY.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Physeal dysplasia (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 5.3: Pre-clinical safety data. Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Adverse effects on cardiac conduction (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Carcinogenicity (Important Potential Risk)	Routine risk minimisation measures: Routine risk communication: SmPC • Section 4.4: Special warnings and precautions for use. • Section 5.3: Pre-clinical safety data. Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Long term safety (Missing Information)	**Routine risk minimisation measures**: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 11.02.2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ezmekly (mirdametinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and as it is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication reflecting the data evaluated is:

"Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above."

3.1.2. Available therapies and unmet medical need

The approach to treatment of the various tumours associated with NF1 depends upon the type of tumour, its effect on adjacent tissues, and related complications. PNs usually involve multiple nerve fascicles, with serpiginous growth and significant vascularity. These lesions can be a significant challenge in surgical treatment and pain management, especially with progressive growth along the spinal column that may result in compression of the spinal cord. There is only one systemic treatment

option approved for patients with NF1 PN: selumetinib (Koselugo), an oral selective MEK inhibitor, approved in the EU in 2021 for the treatment of paediatric patients ≥3 years with NF1 who have symptomatic, inoperable PNs. There are currently no approved treatments for adults or children with NF1 PN under 3 years of age in the EU. Unmet medical need is therefore acknowledged.

3.1.3. Main clinical studies

The pivotal efficacy and safety data in the current application are based on an ongoing open-label, single arm, multi-centre phase I/II study in adult and paediatric participants with NF1-Associated Plexiform Neurofibromas (MEK-NF-201).

This study consists of two phases: the Treatment Phase and the optional Long-Term Follow-Up Phase; the LTFU Phase is currently ongoing. The study treatment consisted of mirdametinib 1 mg and 2 mg capsules and 0.5 mg and 1-mg tablets.

The primary endpoint was defined as the percentage of patients with complete response (CR) or confirmed partial response (PR), with PR defined as target Plexiform Neurofibroma (PN) volume decrease ≥20% at the end of the Treatment Phase compared to baseline. Responses were considered confirmed if the PR was maintained at the subsequent MRI within the 2 to 6 months. Evolution in target PN volume compared to baseline was assessed by a blinded independent central reviewer (BICR). Duration of response (DoR) was a key secondary endpoint.

3.2. Favourable effects

A total of 114 participants (56 paediatrics and 58 adults) with symptomatic inoperable NF1-associated PNs were included in the pivotal study.

The observed Objective Response Rate in target tumour volume compared to baseline as assessed by a blinded independent central reviewer was 51.8 % (95% IC 38.0, 65.3) in the paediatric cohort and 44.1% (95% IC 28.6, 55.1) in the adult cohort, all of them were partial responses (i.e. confirmed volume decrease ≥ 20%).

- 22 (39.3%) participants in the paediatric cohort and 26 (44.8%) participants in the adult cohort had stable disease (volume change < 20%),
- 3 (5.4%) participants in the paediatric cohort and none in the adult cohort had a progressive disease.

The median DoR was not reached for the paediatric cohort as no events of progressive disease (PD) or death after a confirmed response occurred as of the data cut-off and 22 (76%) of paediatric responders were maintaining a confirmed response for at least 12 months.

The median DoR was not reached for the adult cohort as only 1 event of progressive disease after a confirmed response occurred as of the data cut-off and 18 (75%) of adult responders were maintaining a confirmed response for at least 12 months.

3.3. Uncertainties and limitations about favourable effects

- The absence of a randomised comparator and the exploratory nature of pivotal study MEK-NF-201's design are obvious limitations to the interpretation of the study results. It is acknowledged that the natural course of PNs is growth or at best stable over time, therefore, objective responses observed in the pivotal study could in principle be attributed to study treatment.

- The durability of the decrease in target PN volume is uncertain as only data from the 24 cycle treatment phase of the study were provided, the applicant committed to provide an additional 5 years follow-up from the pivotal study as a specific obligation

3.4. Unfavourable effects

About 90% of patients experienced at least one adverse event related to skin disorders (mostly rash and dermatitis acneiform) and 80% to gastrointestinal disorders. Most of the reported adverse events were mild or moderate in severity. Other salient aspects of the safety profile were the ocular toxicity (blurred vision, RVO and RPED), the reported decreased LVEF, and a potential risks of embryofoetal toxicity and carcinogenicity. The exposure to mirdametinib is associated with a number of adverse events leading to dose adjustments (reductions, interruptions, discontinuations respectively in paediatric and adult patients of 12%, 29%, 7% and 20%, 28%, 19%).

3.5. Uncertainties and limitations about unfavourable effects

- The main uncertainties are related to the limited number of patients included in both adult and paediatric cohorts as well as the limited long-term follow-up and the non-controlled results precluding the assessment of relatedness to mirdametinib exposure; the applicant committed to provide an additional 5 years follow-up from the pivotal study MEK-NF-201 and to conduct an non-interventional PASS, listed as specific obligations, in order to confirm the long term safety profile of mirdametinib.
- There are uncertainties on the risk of physeal dysplasia that will be further characterised in the context of an imposed non-interventional PASS
- Furthermore, a genotoxicity risk at the clinical exposure range and a carcinogenicity risk could not be discarded based on the current available data. These risks have been reflected in the RMP (carcinogenicity only) and in the SmPC (genotoxicity and carcinogenicity in sections 4.4 and 5.3) with an appropriate contraception period being recommended (in section 4.6 of the SmPC)

3.6. Effects Table

Table 51: Effects table for mirdametinib

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects – Paediatric cohort (n=56)						
Confirmed Overall Response Rate	Percentage of patients with CR or PR (decrease in volume of target PN by ≥20% compared with baseline)	N (%) [95% CI]	29 (51.8%) [38.0; 65.3]	NA	Uncontrolled study Primary endpoint Review by ICR (not fully blinded to time point)	MEK-NF-201
Duration of Response	DoR≥12 months DoR≥24 months	N (%)	26 (90%) 14 (48%)		Median DoR not reached - Limited follow-up	
Favourable Effects – Adult cohort (n=58)						
Confirmed Overall Response Rate	Percentage of patients with CR or PR (decrease in volume of target PN by ≥20% compared with baseline)	N (%)	24 (41.4%) [28.6;55.1]	NA	Uncontrolled study Primary endpoint Review by ICR (not fully blinded to time point)	MEK-NF-201
Duration of	DoR≥12 months	N	21 (88%)		Median DoR not	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Response	DoR≥24 months	(%)	12 (50%)		reached - Limited follow-up	
Unfavourable Effects – Safety pool (n= 133, Paediatrics n= 58, Adults n= 75)						
Grade 3-4 AEs	Number of patients experiencing an AE	N (%)	Paed: 23 (39.7%) Adult: 25 (33.4%)	N/A	No comparator arm to support causality assessment	Studies MEK-NF-201 and NF-106
Grade 5 AE			Paed: 0 Adult: 1 (1.3%)			
Serious AEs			Paed: 8 (13.8%) Adult: 12 (16.0%)			
AEs leading to discontinuation			Paed: 4 (6.9%) Adult: 12 (16.0%)			
Dermatitis acneiform			Paed: 25 (43.1%) Adult: 62 (82.7%)			
Ejection fraction decreased			Paed: 15 (25.9%) Adult: 9 (12.0%)			
Vision blurred			Paed: 4 (6.9%) Adult:8 (10.7%)			
Retinal vein occlusion			Paed: 0 Adult: 2 (2.7%)			
Retinal pigment epithelium detachment			Paed: 0 Adult: 1 (1.3%)			

Abbreviations: Paed: paediatric

*DCO 20 September 2023, except for DoR based on DCO 12 June 2024

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most relevant effects were the 51.8 % and 44.1% overall response rate in the paediatric and adult cohort respectively when assessed by central BICR readers.

However, the absence of a randomised comparator and the exploratory nature of the pivotal study design are obvious limitations to the interpretation of the study results. It is acknowledged that the natural course of PNs is growth or at best stable over time, therefore, objective responses observed in the pivotal study could in principle be attributed to study treatment. However, due to those limitations, the exact effect of mirdametinib on PN volume is not established.

Regarding clinical outcomes, some improvements were observed, however the non-comparative design of the trial limits the interpretability of those endpoints as patient's and parent's knowledge of treatment assignment may lead to an overestimation of the treatment effect. Furthermore, there is no clear correlation between response and improvement of PROs. Despite those limitations, the considerations from the AHEG consultation received in the context of the Koselugo MAA, could be deemed applicable to Ezmekly, considering the similarities between both products in terms of mechanism of action, indication, and design of the pivotal trial. According to the AHEG, it can be considered plausible that decrease of PN volume is associated with a decrease in symptoms/morbidity and thus that efficacy was shown for the duration of the pivotal trial.

All patients from both cohorts, paediatric and adult, experienced several adverse events. About 90% of the patients experienced at least one adverse event related to skin disorders and about 80% to gastrointestinal disorders. However most of the adverse events were mild or moderate in severity and could be managed by dose modification. The less frequent but potentially severe adverse reactions were the decreased left ventricular ejection fraction and ocular events (including vision blurred, RVO and RPED) which are addressed through recommendations for monitoring before and during the

treatment. Genotoxicity and carcinogenicity risks at the clinical exposure range could not be discarded based on the current data, and are addressed through warnings in the SmPC, an appropriate contraception period being recommended and are reflected in the RMP (only for the carcinogenicity risk). There are remaining uncertainties on the risk of physeal dysplasia. The long-term safety of mirdametinib is presently considered limited and further data are deemed necessary to better understand its safety profile.

3.7.2. Balance of benefits and risks

Considering that the natural course of PNs is growth or at best stability, the observed decreased tumour volume in clinical studies can in principle be attributed to mirdametinib. However, the exact magnitude and duration of the effect of mirdametinib treatment on the volume and growth rate of PNs have not been clearly established due to the absence of a comparator arm and the fact that the pivotal study is still ongoing.

Despite frequent adverse events being reported, those were generally mild and could be managed with dose modification. Taking into account the burden of the disease and the benefit to some patients, the safety profile is considered acceptable. There are remaining uncertainties on the risk of physeal dysplasia and the long-term safety of mirdametinib that will be addressed in the post marketing setting.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating disease. In addition, the product is designated as an orphan medicinal product. Neurofibromatosis type 1 (NF1) is a multisystem disease associated with a lifelong risk of debilitating and potentially life-limiting complications (Oates et al. 2013).). Patients with NF1 develop both benign and malignant tumours at increased frequency throughout life (Gutmann et al. 1997; Seminog et al. 2013). Malignant transformation of tumours may occur in childhood, but more often occurs in adolescence and adulthood. Plexiform neurofibroma represent a major cause of morbidity and disfigurement in individuals with NF1 and, when symptomatic, are associated with increased mortality (Rasmussen et al. 2001; Prada et al. 2012).

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant commits to provide the results of the following specific obligations (SOBs):

  - Efficacy and safety data from the pivotal study MEK-NF-201 with a longer follow-up. At the original study MEK-NF-201 data cut-off (20 September 2023), the median (min, max) duration of mirdametinib exposure was 21.8 (0.4, 45.6) months. The applicant proposes an additional data cut-off on 22 December 2028 that will provide an additional 5 years of follow-up data.

In the current application, the median duration was not yet reached and is considered necessary to achieve comprehensiveness of the data package. As such, provision of an additional 5 years of follow-up from the pivotal study will further characterise the duration of response, to confirm the long term benefit of mirdametinib in patients responding to treatment, and will allow a better characterisation of the long-term safety profile of the product.

- Safety data from a non-interventional post-authorisation safety study (PASS). The PASS patient population is planned to include NF1 patients in the European Union (EU) and the United States with symptomatic PN who have been prescribed at least one dose of mirdametinib and who are aged ≥2 years at the start of treatment.

  This PASS will provide the safety data from an additional 60 patients aged 2 to < 18 years and 40 adult patients (aged ≥ 18 years) and allow a better characterisation of the long-term safety profile of the product.

  Based on the above, the CHMP considered that the additional 5 years of follow-up date for study MEK-NF-201 and the results of the non-interventional PASS is likely to provide comprehensive data suitable to confirm the positive benefit-risk balance of mirdametinib.

- Unmet medical needs will be addressed.
- In adults and in patients between 2 and 3 years of age with symptomatic, inoperable NF1 PNs, there is currently no authorised treatment. There is also no formulation available for patients unable or unwilling to swallow the capsule whole. In the population of paediatric patients aged ≥3 years, there is currently one conditionally authorised treatment, Koselugo (selumetinib). In this patient population, mirdametinib is considered to address the unmet medical need to a similar or greater extent than Koselugo. The comparison of the results from study MEK-NF-201 to the SPRINT data suggests that the confirmed ORR by ICR for mirdametinib is at least equivalent to selumetinib (52% [38;65] vs 44% [30;59]), with similar proportion of patients sustaining a response ≥ 12 months (90% vs 82%). Furthermore, based on the limited available data, the toxicities of mirdametinib appear overall comparable or improved when compared with selumetinib, with a rate of Grade ≥3 treatment-emergent adverse events of 39.3% vs 62%, serious adverse events of 14.3% vs 24%, and a rate of AE leading to discontinuation of 8.6% vs 12.2%.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Given the absence of authorised products for the treatment of inoperable PN in adults and in paediatric patients aged ≥2 years with NF1, an orphan indication, the benefits to public health of the immediate availability of mirdametinib outweigh the risks.

3.8. Conclusions

The overall benefit/risk balance of Ezmekly is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ezmekly is not similar to Koselugo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ezmekly is favourable in the following indication:

"Ezmekly as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above."

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the efficacy and safety of mirdametinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should submit an updated analysis of the study MEK-NF-201 with a data cut-off of 22 December 2028 that will provide an additional 5 years of follow-up.	June 2029
Non-interventional post-authorisation safety study (PASS): In order to confirm the long-term safety of mirdametinib, in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above, the MAH should conduct and submit the results of a study conducted in patients with NF1 who have been prescribed at least one dose of mirdametinib and who are aged 2 and above at the start of mirdametinib.	August 2033

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that mirdametinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed paediatric investigation plan P/0223/2024; the results of these studies are reflected in the summary of product characteristics (SmPC) and, as appropriate, the package leaflet.