26 January 2017
EMA/346029/2017
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Simulect

basiliximab

Procedure no.: EMA/H/C/000207/P46 044

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2017. Reproduction is authorised provided the source is acknowledged.

Table of contents

1. Introduction 3

2. Scientific discussion 3

2.1. Information on the development program 3
2.2. Information on the pharmaceutical formulation used in the study 5
2.3. Clinical aspects 5
2.3.1. Introduction 5
2.3.2. Clinical study 5
2.3.3. MAH's Discussion on clinical aspects 17

3. Rapporteur's overall conclusion and recommendation 18

1. Introduction

On 10 October 2016, the MAH submitted data from paediatric patients included in

Study CCHI621ADE04: A multicenter, open-label, randomized, two arm study to investigate the efficacy and safety of a therapy avoiding intraoperative steroids in combination with Simulect®, Sandimmun®/ Sandimmun® Optoral and steroids in pediatric de novo liver transplant recipients (SINTRA)

in accordance with Article 46 of Regulation (EC) No1901/2006.

A short Critical Expert Overview has also been provided. The MAH states that the submitted paediatric study does not modify the benefit-risk assessment of Simulect in the approved indication and that therefore no consequential regulatory action is required.

2. Scientific discussion

2.1. Information on the development program

Product

Basiliximab is a murine/human chimeric monoclonal antibody (IgG1κ) that is directed against the interleukin-2 receptor alpha-chain (CD25 antigen), which is expressed on the surface of T-lymphocytes in response to antigenic challenge. It specifically binds with high affinity to the CD25 antigen on activated T-lymphocytes expressing the high affinity interleukin-2 receptor and thereby prevents binding of interleukin-2, the signal for T-cell proliferation.

Authorisation details

The European Commission granted a marketing authorisation valid throughout the European Union for Simulect to Novartis Europharm Limited on 9 October 1998. The approval to market a medicine in one, several or all European Union Member States. was renewed on 9 October 2003 and on 9 October 2008.

Therapeutic Indications

Simulect is indicated for the prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years). It is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil.

Clinical studies

The efficacy of basiliximab in prophylaxis of organ rejection in *de novo* renal transplantation has

been demonstrated in double-blind placebo-controlled studies. Results from two pivotal 12-month multicentre studies (722 patients in total) comparing basiliximab with placebo show that basiliximab, used concomitantly with ciclosporin for microemulsion and corticosteroids, significantly reduces the incidence of acute rejection episodes both within 6 (31% vs. 45%, p<0.001) and 12 (33% vs. 48%, p<0.001) months after transplantation. There was no significant difference between basiliximab and placebo-treated patients in graft survival after 6 and 12 months (at 12 months 32 graft losses on basiliximab (9%) and 37 graft losses on placebo (10%)). The incidence of acute rejection episode was substantially lower in patients receiving basiliximab and a triple drug immunosuppressive regimen. Results from two multicentre double-blind studies comparing basiliximab with placebo (463 patients in total) show that basiliximab significantly reduces the incidence of acute rejection episodes within 6 months after transplantation when used concomitantly with ciclosporin for microemulsion, corticosteroids, and either azathioprine (21% vs. 35%) or mycophenolate mofetil (15% vs. 27%). Graft loss occurred in 6% of basiliximab-treated and 10% of placebo-treated patients by 6 months. The adverse event profile remained comparable between treatment groups.
In a pooled analysis of two five-year open-label extension studies (586 patients total) the combined graft and patient survival rates were not statistically different for the basiliximab and placebo groups. Extension studies also showed that patients who experienced an acute rejection episode during the first year after transplantation experienced more graft losses and deaths over the five-year follow-up period than patients who had no rejection. These events were not influenced by basiliximab.

Paediatric population
The efficacy and safety of basiliximab were evaluated in two paediatric studies.
Basiliximab was used concomitantly with ciclosporin for microemulsion and steroids in an uncontrolled study in 41 paediatric *de novo* renal transplant recipients. Acute rejection occurred in 14.6% of patients by 6 months post-transplantation, and in 24.3% by 12 months. Overall the adverse event profile was consistent with general clinical experience in the paediatric renal transplantation population and with the profile in the controlled adult transplantation studies.
A 12-month, randomised, placebo-controlled, double-blind, multicentre study investigated basiliximab in combination with ciclosporin for microemulsion, mycophenolate mofetil and steroids in paediatric renal allograft recipients. The primary objective of the study was to demonstrate superiority of this combination versus treatment with ciclosporin for microemulsion, mycophenolate mofetil and steroids in the prevention of acute rejections. Of the 202 patients, 104 were randomised to basiliximab and 98 to placebo. The primary efficacy endpoint, time to first biopsy-proven acute rejection (BPAR) episode or treatment failure defined as graft loss, death or presumptive rejection within the first 6 months post transplantation, occurred in 16.7% of basiliximab-treated patients and 21.7% of placebo-treated patients. When borderline rejections were included in the primary efficacy endpoint, the rates were 26.0% and 23.9% respectively, with no statistically significant difference between the basiliximab- and placebo-treated groups (HR: 1.04, 90% CI: [0.64; 1.68]). The rates of BPAR were 9.4% in the basiliximab group and 17.4% in the placebo group (HR: 0.50, 90% CI: [0.25; 0.99]). When borderline rejections were included, the rates were 20.8% and 19.6% respectively (HR:

1.01, 90% CI: [0.59; 1.72]). The overall safety profiles were similar in both groups. The incidence rates of adverse events and the pattern of adverse events were comparable between the two treatment groups and to be expected for the treatment regimens and the underlying diseases.

2.2. Information on the pharmaceutical formulation used in the study

Simulect® (not registered for pediatric de novo liver transplant patients) was part of the triple-immunosupression therapy regimen, which was investigated during the study period and was therefore defined as study medication. Simulect® (10 mg) was supplied as a lyophilisate in vials with ampoules of sterile water for injection (5 mL) and had to be given of 10 mg (body weight <35 kg) or 20 mg (body weight ≥35 kg) strength. The first dose had to be given on day 0 within 8 hours of reperfusion of the graft. The second dose had to be given on the morning of day 4. Each dose was administered by i.v. bolus injection.

2.3. Clinical aspects

2.3.1. Introduction

As part of a remediation exercise, which reviewed all interventional and non-interventional studies with pediatric patients in scope of the Article 46 requirement, the Simulect study CCHI621ADE04 (SINTRA study) has been identified for an Article 46 submission.

2.3.2. Clinical study

Description

Study **CCHI621ADE04 (SINTRA-Study)** was a German multicenter, open-label, randomized, two arm study comparing the efficacy and safety of a regimen combining Simulect®, Sandimmun®/ Sandimmun® Neoral (named Sandimmun Optoral® in Germany) and steroids with and without intraoperative steroids in pediatric de novo liver transplant recipients.

First patient recruited: 20 March 2004
Last patient completed: 09 March 2009

A total of 77 patients were enrolled (37 males, 40 females). Patients' mean age (±SD) was 3.4 ± 4.7 years and 58.4% belonged to the stratum <2 years. A total of 73 patients received two doses of

Simulect given at day 0 and day 4, of whom 64 received the 10 mg dose, while 4 patients received only one dose of 10 mg at day 0.

Methods

Objectives

The primary objective of this study was to compare the effect of an immunosuppressive therapy administered with intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/ Sandimmun® Optoral and steroids, as measured by the incidence of at least one biopsy proven acute rejection episode, graft loss, or death within the first three months post-transplantation in pediatric de novo liver transplant recipients.

The secondary objectives of this study were:

- To evaluate the effect of a regimen with intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids as measured by the incidence of biopsy proven acute rejection episodes within the first three months.
- To evaluate the efficacy of a regimen with intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids as measured by the incidence of steroid resistant rejection episodes within three and six months.
- To evaluate the proportion of patients experiencing death or graft loss (defined as being listed for a re-transplantation) treated with a regimen consisting of intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids within three and six months post-transplantation.
- To evaluate the safety of a regimen with intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids as measured by the incidence of bacterial, viral and fungal infections during six months.
- To evaluate the effect of a regimen with intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids as measured by the time to onset of a first biopsy proven acute rejection.
- To evaluate the proportion of patients with treatment failure treated with a therapy consisting of intraoperative versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids within three and six months.
- To evaluate the incidence of biopsy proven acute rejection episodes, graft loss or death depending on CsA morning trough level (C-0h), CsA level taken 2 hours after morning dose (C-2h) and AUC0-6h as well as to evaluate the correlations of AUC0-6h with C-0h and C-2h.

Study design

This was a national, 6 months, multicenter, open-label, randomized study comparing the effect and safety of a therapy regimen with versus without intraoperative steroids in combination with Simulect®, Sandimmun®/Sandimmun® Optoral and steroids in pediatric *de novo* liver transplant recipients.

A total of 80 patients were planned to be enrolled. After a screening visit the patients' randomization was performed before transplantation (day 0). Age strata were <2 years and 2-16 years (1:1 ratio). Subsequent visits were performed at days 1, 4, 7, 14, 28 and months 3 and 6. Liver biopsies and suspected rejection episodes were documented during this study period as well as CsA levels. In case of previous study discontinuation data of acute rejection periods were collected by follow-up forms scheduled to be completed at months 3 and 6.

Treatment regimen

Investigational drug:

Simulect® (not registered for pediatric *de novo* liver transplant patients) was part of the triple-immunosupression therapy regimen, which was investigated during the study period and was therefore defined as study medication. Simulect® (10 mg) was supplied as a lyophilisate in vials with ampoules of sterile water for injection (5 mL) and had to be given of 10 mg (body weight <35 kg) or 20 mg (body weight ≥35 kg) strength. The first dose had to be given on day 0 within 8 hours of reperfusion of the graft. The second dose had to be given on the morning of day 4. Each dose was administered by i.v. bolus injection.

Immunosupressive treatment:

Patients of both treatment groups had to be treated with Simulect® (at day 0 and day 4 as described above). Sandimmun®/Sandimmun® Optoral had to be started with 100 mg/m²/day i.v. (2x4h) for 7 days and was to be continued i.v. or p.o. from day 8 onwards as per center practice (with dose increase by factor three in case of switch from i.v. to p.o.). During the 6 months treatment period Sandimmun® doses had to be adjusted according to CsA-trough levels.

Intravenous prednisolone (loading dose: 300 mg/m2, maximum 500 mg) had to be administered intraoperatively only in group 1 (day 0). The first dose of steroids in group 2 (day 0) had to be administered within 8 hours after reperfusion of the graft. Beginning from day 1 to day 6 doses of 15 mg/m2/day had to be given i.v. in both study groups. Then, the steroid doses (oral prednisone or its equivalent) were to be decreased from 10 mg/m²/day p.o. (day 7-13), to 7.5 mg/m²/day p.o. (day 14- 30), to 4 mg/m²/day p.o. (until end of month 2), to 2.5 mg/m²/day p.o. (until end of month 3) and to 1 mg/m²/day p.o. (until end of month 6). If steroids were not tolerated orally beyond day 6, they were to be given intravenously.

Study population /Sample size

Number of patients:

A total of 77 patients were screened and treated with study medication (with 59.7% completing the study).

Study population:

The study population consisted of male and female patients, age ≤16 years, who were scheduled to undergo a primary orthotopic liver transplantation (whole organ or split liver or reduced size). Inclusion criteria were: cadaveric or living donor grafts, (from both related and unrelated donors), exclusion of pregnancy/use of contraceptive measures, cold ischemia time <12 hours, and informed consent of the parents/patients.

Exclusion criteria were:

multiple solid organ transplants or/and previous receipt of transplanted organs, auxiliary liver transplant recipients, fulminant hepatic failure, autoimmune hepatitis, primary sclerosing cholangitis, severe acute systemic infections, hepatitis B surface antigen/HCV/HIV positive, known contraindication to i.v. or p.o. cyclosporine or corticoids, non-ability to comply with the protocol, relevant abnormal physical or laboratory findings within 2 weeks of inclusion, relevant severe allergy, hypersensitivity to Simulect® or similar drugs, history/presence of relevant malignancy, pregnancy/breastfeeding, and use of any investigational or immunomodulatory/immunosuppressive drug within 4 weeks prior to transplantation.

Outcomes/endpoints/Statistical Methods

Safety assessments

Safety was assessed by the incidence, nature and severity of adverse events and serious adverse events.

Efficacy assessments

Efficacy was assessed by the

- Incidence of at least one biopsy proven acute rejection episode (BPAR), graft loss or death within the first three months post-transplantation.
- Incidence of BPAR within the first three months.
- Incidence of steroid resistant rejection episodes within three and six months.
- Proportion of patients experiencing death or graft loss (defined as being listed for a retransplantation) within three and six months post-transplantation.
- Incidence of bacterial, viral and fungal infections during six months.
- Time to onset of a first biopsy proven acute rejection.
- Proportion of patients with treatment failure within three and six months.
- Incidence of BPAR, graft loss or death depending on C-0h, C-2h and AUC0-6h.

Results

Recruitment / Number analysed

All screened patients were randomized and received study medication. In the treatment group without intraoperative steroids more patients dropped out because of adverse events (21.1% vs. 2.6%; cf. PTT 7.1-2). The patient disposition is shown in Table 1.

Table 1 Patient disposition (safety/ITT population)

	With intraoperative steroids	Without intraoperative steroids	All patients
Number (%) of patients			
Screened	39 (100.0)	38 (100.0)	77 (100.0)
Treated	39 (100.0)	38 (100.0)	77 (100.0)
Completed	26 (66.7)	20 (52.6)	46 (59.7)

Source: Post-text table 7.1-1

A total of 20 protocol violations were noted in 19 patients (24.7%), with 10 patients (13.0%) showing protocol violations that were considered "major" and therefore led to exclusion from the per protocol analysis data set (multiple specifications were possible, cf. PTT 7.2-1).

Because the primary analysis was to be performed on the intent-to-treat population (identical to the safety population), the results presented in this report are based on the Safety/ITT analysis set. For the results found in the per-protocol analyses please refer to the respective post-text tables.

Baseline data

Age

The patients' mean age was 3.4 ± 4.7 years, 58.4% belonged to the stratum younger than 2 years. A similar proportion of boys and girls participated in this study (48.1% vs. 51.9; cf. PTT 7.4-1.1.1.a). Table 2 summarizes the demographic characteristics of the study patients.

Table 2	Demographic characteristics (safety/ITT population)		
	With intraoperative steroids (N=39)	Without intraoperative steroids (N=38)	All patients (N=77)
Sex - n (%)			
Male	18 (46.2)	19 (50.0)	37 (48.1)
Female	21 (53.8)	19 (50.0)	40 (51.9)
Race - n (%)			
Caucasian	36 (92.3)	33 (86.8)	69 (89.6)
Oriental	2 (5.1)	4 (10.5)	6 (7.8)
Other	1 (2.6)	1 (2.6)	2 (2.6)
Age (years)			
Mean ± SD	3.08 ± 4.09	3.71 ± 5.36	3.39 ± 4.74
Median	1	1	1
Range	0 - 14	0 - 17	0 - 17
Age strata - n (%)			
< 2 years	21 (53.8)	24 (63.2)	45 (58.4)
2-16 years	18 (46.2)	14 (36.8)	32 (41.6)
Source: Post-text table 7.4-1.1.1a			

End stage disease leading to transplantation

The most frequent end stage disease was extrahepatic biliary atresia. The proportion of this end stage disease was higher in the younger than in the older stratum (86.7% versus 25.0%, with an overall proportion of 61.0%, cf. PTT 7.4-2.3.1).

Table 3 End stage disease leading to transplantation (safety/ITT population)

	With intraoperative steroids (N=39), n (%)	Without intraoperative steroids (N=38), n (%)	All patients (N=77), n (%)
Extrahepatic biliary atresia	27 (69.2)	20 (52.6)	47 (61.0)
Intrahepatic biliary hypoplasia	1 (2.6)	3 (7.9)	4 (5.2)
Progressive familiar intrahepatic cholestasis	3 (7.7)	5 (13.2)	8 (10.4)
Metabolic disorder with diseased liver	2 (5.1)	1 (2.6)	3 (3.9)
Unknown origin	0	1 (2.6)	1 (1.3)
Other	6 (15.4)	8 (21.1)	14 (18.2)

Source: Post-text table 7.4-2.3.1

Relevant medical history/current medical conditions

All patients (100%) had a relevant medical history or current medical condition, which was active in most of the patients (95%).

Prior/Concomitant medications

About one fifths of the patients received prior medications or non-drug therapies (with intraoperative steroids: 23.1%, without intraoperative steroids: 15.8%, cf. PTT 7.4-4.1.1.a). Concomitant medications were administered to all patients (particularly medications referring to the ATC groups "alimentary tract and metabolism", "anti-infectives for systemic use", "blood and blood forming organs", "cardiovascular system", "dermatologicals", and "nervous system"; cf. PTT 7.4-4.2.1.a).

Cold ischemia time

The mean cold ischemia time was 7.82 ± 3.67 hrs, with comparable values in both treatment groups but higher values in the stratum of older patients (<2 years: 6.91 ± 3.78 hrs vs. 2-16 years: 9.09 ± 3.15 hrs; cf. PTT 7.4-5.2).

Study medication and immunosuppressive treatment

Most patients received a Simulect® dose of 10 mg, nine patients received 20 mg. Four patients received Simulect® only at day 0 (cf PTT 8.1.-1), two of them by mistake and two of them because of study discontinuation. The younger patients received lower doses of immunosuppressive treatment (cf. PTT 8.1-1, 8.2-1, 8.3.1).

Table 4 **Study drug administration and immunosuppressive treatment (safety/ITT population)**

	With intraoperative steroids (N=39), n (%)	Without intraoperative steroids (N=38), n (%)	All patients (N=77), n (%)
Dosage of Simulect® at day 0			
10 mg	34 (87.2)	34 (89.5)	68 (88.3)
20 mg	5 (12.8)	4 (10.5)	9 (11.7)
Dosage of Simulect® at day 4			
10 mg	32 (86.5)	32 (88.9)	64 (87.7)
20 mg	5 (13.5)	4 (11.1)	9 (12.3)
Dosage of intraoperative steroids® (mg)			
mean ± SD	185 ± 120.8	n.a.	185 ± 120.8
Average daily dose of Sandimmun®/Sandimmun® Optoral (mg)			
mean ± SD	55.16 ± 36.22	58.18 ± 42.63	56.65 ± 39.28

Source: Post-text table 8.1-1, 8.2-1, 8.3-1.1

n.a.: not applicable

Efficacy results

Primary objective

The primary objective of this study was to evaluate the effect of an immunosuppressive therapy avoiding intraoperative steroids measured by the incidence of at least one BPAR, graft loss or death within the first three months post-Tx.

The incidence of the primary composite endpoint (i.e., BPAR, graft loss, or death within 3 months after Tx) was higher in the group without intraoperative steroids (68.4% versus 56.4%, p=0.35, cf. PTT 9.1-1.1, PTT 9.1.-3.1). These results were confirmed by the sensitivity analysis performed in the per-protocol population (75.8% versus 55.9%, p=0.12; cf. PTT 9.1-1.2, PTT 9.1.-3.2). Treatment differences were more pronounced in the younger patients (<2 years: 62.5% vs. 42.9% and 2-16 years: 78.6% vs. 77. 8%; cf. PTT 9.1-2.1) who showed higher incidence rates for BPAR, graft loss or death in both treatment groups.

These results of the primary endpoint analysis are summarized in Table 5.

Table 5 Primary endpoint (safety/ITT population)

Incidence of BPAR, graft loss, of death within the first 3 month after Tx	With intraoperative steroids , n (%)	Without intraoperative steroids , n (%)	Difference between treatment groups, % (p-value)
Time to event (months), median[§]	1.44	0.75	0.95 (p=0.29)[‡]
Incidence			
Total (N=39, 38)	22 (56.4%)	26 (68.4%)	12.0% (p=0.35)[†]
Stratum age < 2 years (N=21, 24)	8 (38.1)	15 (62.5)	24.4% (p=0.14)[†]
Stratum age 2-16 years (N=18, 14)	14 (77.8%)	11 (78.6%)	0.8% (p=1.0)[†]

Source: Post-text table 9.1-1.1, 9.1-3.1, 9.1-5.1

†: Fisher's exact test

‡: Log-rank test

§: Kaplan-Meier estimates were calculated for the total stratum only

Secondary objectives

During the whole study period, BPAR was observed in 47 patients, with a higher incidence among the patients without intraoperative steroids (53.8% vs. 68.4%). The median for the time to BPAR was 1.93 months and 0.75 months (intraoperative steroids vs. without intraoperative steroids, log-rank test: p=0.14; cf. PTT 9.1-5.4).

The results of the secondary parameters are summarized in Table 6.

Table 6 Secondary endpoints (safety/ITT population)

	With intraoperative steroids (N=39), N (%)	Without intraoperative steroids (N=38), n (%)	Difference between treatment groups % (p-Value*)
Incidence of event within the first 3 months post Tx			
BPAR	20 (51.3)	26 (68.4)	-17.1 (0.16)
Graft loss	2 (5.1)	1 (2.6)	2.5 (1.0)
Death	0 (0.0)	1 (2.6)	-2.6 (0.49)
Steroid resistant rejection episode	2 (5.13)	2 (5.26)	0.13 (1.0)
Treatment failure	2 (5.13)	2 (5.26)	0.13 (1.0)
Incidence of event within the first 6 months post Tx			
BPAR	21 (53.8)	26 (68.4)	-14.6 (0.24)
Graft loss	2 (5.1)	2 (5.3)	-0.1 (1.0)
Death	0 (0.0)	1 (2.6)	-2.6 (0.49)
Steroid resistant rejection episode	2 (5.13)	2 (5.26)	0.13 (1.0)
Treatment failure	2 (5.13)	2 (5.26)	0.13 (1.0)

Source: Post-text table 9.1-1.1, 9.1-2.1, 9.1-3.1, 9.1-4.1, 9.2-1.1, 9.2-1.2, 9.2-2.1, 9.2-2.2, 9.3-1.1, 9.3-1.2, 9.3-2.1, 9.3-2.2

*Fischer's exact test

A total of 83.1% of the patients suffered from an infection (without intraoperative steroids: 89.5% vs. with intraoperative steroids: 76.9%; cf. PTT 10.2-6.1). Fungal infections were present in 42.1% vs. 41.0%, viral infections in 36.8% vs. 38.5%, and bacterial infections in 47.4% vs. 25.6% (without intraoperative steroids vs. with intraoperative steroids; cf. PTT 10.2-6.2).

Safety results

Methods and variables

The assessment of safety was based on the frequency of treatment emergent adverse events and on the number of laboratory values outside the pre-determined ranges. Treatment emergent adverse events were coded according to MedDRA terminology and displayed in the tabulated summaries.

Adverse events which were not treatment emergent were listed only (not described in this report). The safety results are presented for the ITT/safety population (N=77).

Adverse events (i.e., treatment emergent AE)

All patients in the safety population experienced at least one (treatment emergent) adverse event (cf. PTT 10.1-1). 42.9% of the patients suffered from an AE with "severe" intensity (47.4% of the patients with intraoperative steroids vs. 38.5% of the patients without intraoperative steroids; cf. PTT 10.1-3). Approx. half of the patients experienced AEs suspected to be study drug related (48.7% vs. 47.4%; most frequently infections and infestations; cf. PTT 10.1-4).

All AEs with an incidence of ≥10% at primary SOC level are summarized in text Table 7.

Table 7 Number (%) of patients with most frequently reported (>10%) AEs by MedDRA primary SOC (safety/ITT population)

	With intraoperative steroids (N=39), n (%)	Without intraoperative steroids (N=38), n (%)	All patients (N=77), n (%)
Number (%) of patients with AE(s)	39 (100.0)	38 (100.0)	77 (100.0)
MedDRA Primary System Organ Class (PSOC)			
Gastrointestinal disorders	35 (89.7)	36 (94.7)	71 (92.2)
Infections and infestations	30 (76.9)	34 (89.5)	64 (83.1)
Metabolism and nutrition disorders	30 (76.9)	33 (86.8)	63 (81.8)
Vascular disorders	33 (84.6)	30 (78.9)	63 (81.8)
General disorders and administration site conditions	26 (66.7)	31 (81.6)	57 (74.0)
Respiratory, thoracic and mediastinal disorders	24 (61.5)	30 (78.9)	54 (70.1)
Investigations	28 (71.8)	26 (68.4)	54 (70.1)
Blood and lymphatic system disorders	21 (53.8)	26 (68.4)	47 (61.0)
Hepatobiliary disorders	18 (46.2)	18 (47.4)	36 (46.8)
Injury, poisoning and procedural complications	13 (33.3)	18 (47.4)	31 (40.3)
Psychiatric disorders	12 (30.8)	17 (44.7)	29 (37.7)
Skin and subcutaneous tissue disorders	7 (17.9)	9 (23.7)	16 (20.8)
Renal and urinary disorders	12 (30.8)	13 (34.2)	25 (32.5)
Cardiac disorders	8 (20.5)	9 (23.7)	17 (22.1)
Endocrine disorders	4 (10.3)	4 (10.5)	8 (10.4)
Nervous system disorders	2 (5.1)	4 (10.5)	6 (7.8)
Immune system disorders	0 (0.0)	4 (10.5)	4 (5.2)

Source: Post-text table 10.1-2

Deaths and other serious adverse events

A summary of deaths, other serious adverse events (SAEs) or other significant AEs is provided in PTT

10.2-1 and Table 8.

Table 8 Number (%) of patients who died, had other serious or clinically significant AEs or discontinued because of them (safety/ITT population)

Number (%) of patients with	With intraoperative steroids (N=39), n (%)	Without intraoperative steroids (N=38), n (%)	All patients (N=77), n (%)
Any serious AE	18 (46.2)	23 (60.5)	41 (53.2)
Any fatal SAE	0 (0.0)	1 (2.6)	1 (1.3)
Any non-fatal SAE	18 (46.2)	23 (60.5)	41 (53.2)
Any non-fatal SAE causing premature discontinuation of study drug	3 (7.7)	3 (7.9)	6 (7.8)
Any non-fatal SAE causing adjustment/temporary interruption of study drug	0 (0.0)	0 (0.0)	0 (0.0)
Any non-serious AE requiring premature discontinuation	1 (2.6)	6 (15.8)	7 (9.1)
Any non-serious AE requiring adjustment/temporary interruption of study drug	1 (2.6)	5 (13.2)	6 (7.8)
Source: Post-text table 10.2-1			

In the treatment group without intraoperative steroids more patients experienced a serious (non-fatal) AE (60.5% vs. 46.2%), prematurely discontinued the study (15.8% vs. 2.6%), or had an adjustment or temporary interruption of the study medication due to a non-serious AE (13.2% vs. 2.6%, cf. PTT 10.2-1). Regarding the stratum of younger patients a high incidence of serious AE was observed in the treatment group without intraoperative steroids (70.8% vs. 52.4%; cf. PTT 10.2-1.b).

One 14-year old boy (without intraoperative steroids) died because of uncontrolled bleeding/haemorrhage 27 days after transplantation. The investigator did not suspect a causal relationship to the study medication (10.2-2).

Laboratory values

Laboratory values changed during the study course similarly in both treatment groups (see section 10.3 of post-text tables).

Pharmacology:

The incidence of BPAR, graft loss or death was presented by categories of C-0h and C-2h and AUC 0-6h. Here, the first measured CsA levels of each patient were used to dichotomize the treatment groups

by median split (within treatment groups, because of the intraoperative steroid administration in one group). As an exception no age stratification was provided for this analysis.

The influence of C-0h, C-2h and AUC0-6h on the primary efficacy endpoint was evaluated by a logistic regression modeling "incidence on BPAR, graft loss or death" as dependent variable and "C-0h", "C-2h" or "AUC0-6h" as independent variables.

No influence of C-0h, C-2h, or AUC 0-6h was found (p=0.88, p=0.68, and p=0.14; cf. PTT 9.1-6.7).

2.3.3. MAH's Discussion on clinical aspects

This study was terminated after the randomization of 77 patients (planned=80 patients). 59.7% of the patients completed the study. For the per-protocol analysis which was performed as sensitivity analysis, N=58 patients were available. The primary analysis was based on the intent-to-treat population which comprised N=77 patients and was identical to the safety population.

The patients' mean age was 3.4 ± 4.7 years, 58.4% belonged to the stratum <2 years. The incidence of the composite primary endpoint (BPAR, graft loss, or death within 3 months post Tx) was descriptively higher in the group which avoided intraoperative steroids (68.4% versus 56.4%) and resulted in a p-value of p=0.35 (Fisher's exact test). These results were confirmed by the sensitivity analysis evaluating the per-protocol population (75.8% versus 55.9%, p=0.12). In the stratum of patients younger than 2 years more events of the primary endpoint occurred in the treatment group avoiding intraoperative steroids (62.5% vs. 42.9) while patients aged 2-16 years showed similar rates in both treatment groups (78.6% vs. 77.8%; patients without intraoperative steroids vs. patients with intraoperative steroids), but the incidence rates were higher than for the younger patients.

The incidence of infections was descriptively higher in the group avoiding intraoperative steroids (89.5% versus 76.9%). In the age stratum 2-16 years a similar rate of infections was observed in both treatment groups (72.2% vs. 78.6%, with intraoperative steroids mentioned first). In the stratum < 2 years more infections were observed for the treatment group avoiding steroids (81.0% vs. 95.8%, with intraoperative steroids mentioned first) and the incidence rates were higher than for the older patients.

A serious adverse event occurred more often in patients treated without intraoperative steroids (60.5% vs. 46.2%). In the age stratum 2-16 years SAE incidences were similar in both treatment groups (42.9% vs. 38.9%, without intraoperative steroids mentioned first). The younger stratum showed higher SAE incidences in the treatment group avoiding steroids (70.8% vs. 52.4%; without intraoperative steroids mentioned first) and the incidences rates were higher than for the older patients.

Neither CsA morning trough level (C-0h) nor the level taken 2 hours after morning dose (C-2h) nor the AUC 0-6h showed an influence on the primary efficacy variable BPAR, graft loss or death within the first 3 months post Tx.

Thus, the investigated study regime – avoiding intraoperative steroids in a post-transplant triple-immunosuppressive therapy consisting of Simulect®, Sandimmun®/Sandimmun® Optoral and steroids in pediatric *de novo* liver transplant recipients – lead to a descriptively increased rate of biopsy proven acute rejection episodes, graft loss or death within the first 3 months post transplantation. This

disadvantage was caused by the stratum of patients younger than 2 years while patients aged 2-16 years showed similar incidence rates in both treatment groups.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted data from pediatric patients included in Study CCHI621ADE04, a multicenter, open-label, randomized, two arm study to investigate the efficacy and safety of a therapy avoiding intraoperative steroids in combination with Simulect®, Sandimmun®/ Sandimmun® Optoral and steroids in pediatric de novo liver transplant recipients (SINTRA).

The study population of pediatric de novo liver transplant recipients evaluated in this study is different to the population of de novo renal transplant recipients Simulect has been approved for.

Data interpretation is limited based on the relatively low number of patients, especially in the group of patients aged 2-16 years. However, study results indicate that the avoidance of intraoperative steroids is associated with an increase in infections, biopsy proven acute rejection episodes, graft loss or death within the first 3 months post transplantation in patients <2 years of age.

Benefit-risk-assessment

Based on the data submitted, the benefit/risk profile of Simulect in paediatric subjects in the approved indication (prophylaxis of acute organ rejection in *de novo* allogeneic renal transplantation in adult and paediatric patients (1-17 years), to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immunosuppression, in patients with panel reactive antibodies less than 80%, or in a triple maintenance immunosuppressive regimen containing ciclosporin for microemulsion, corticosteroids and either azathioprine or mycophenolate mofetil) remains unchanged.

☒ Fulfilled:

No regulatory action required.