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

Simulect

BASILIXIMAB

Procedure no: EMEA/H/C/000207/P46/042

Note

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

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Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Simulect

(Basiliximab)

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

Marketing authorisation holder (MAH): Novartis

Rapporteur:	Jan Müller-Berghaus
Start of the procedure:	22/03/2015
Date of this report:	21/04/2015
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Need for plenary discussion	No

Administrative information

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1. Introduction

On February 19 2015, the MAH submitted data from paediatric patients included in study CCHI621A1401 and CCHI621AJP01 in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided. The MAH stated that the submitted paediatric study does not influence the benefit risk for Simulect and that there is no consequential regulatory action.

2. Scientific discussion

2.1. Information on the development program

Studies CCHI621A1401 and CCHI621AJP01 were conducted solely in Japan. Both studies are Novartis sponsored Japanese studies and were conducted for purposes of providing postmarketing surveillance data in Japanese patients to comply with post-marketing requirements. Study CCHI621A1401 was a paediatric study with 76 patients included in the safety/efficacy set.

In study CCHI621AJP01 a total of 1599 patients from 56 study sites were enrolled.

2.2. Information on the pharmaceutical formulation used in the studies.

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 Tlymphocytes 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.
Simulect is indicated for the prophylaxis of acute organ rejection in de novo renal transplantation in adult and paediatric patients.
The standard total dose is 40 mg, given in two doses of 20 mg each. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The second 20 mg dose should be given 4 days after transplantation. In paediatric patients weighing less than 35 kg, the recommended total dose is 20 mg, given in two doses of 10 mg each. In paediatric patients weighing 35 kg or more, the recommended dose is the adult dose, i.e. a total dose of 40 mg, given in two doses of 20 mg each.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final reports for two Japanese post-marketing surveillance studies:

- Special Drug use result survey of Simulect 10mg in pediatric renal transplantation study CCHI621A1401;
- Drug Use Observational Study on Simulect® 20mg, Study CCHI621AJP01

2.3.2. Clinical studies

CCHI621A1401: Special Drug use result survey of Simulect 10mg in pediatric renal transplantation study

Description

PMS study CCHI621A1401 was conducted in a pediatric kidney transplant population and included 80 patients who received two doses of 10 mg Simulect intravenously. Patients were followed for at least 6 months and up to 5 years post-transplantation.

Out of the 80 patients enrolled, data were available for analysis in 76. There were 43 males and 33 females (43%). Mean age (±SD) was 7.4±3.6 years (range 1 to 17 years). Eight patients were 2 year-old or younger, 18 had between 3 and 5 years, 36 between 6 and 10 years and 9 were 11-year old or older.

Methods

Objectives

The objectives of this study is to collect data to confirm the safety and efficacy of Simulect 10 mg for pediatric intravenous injection (hereinafter called the drug) under the actual medical practice, to grasp the problems in order to apply to the Ministry of Health, Labor and Welfare for re-examination on the following post approval commitment.

Study design

The observation period after drug delivery : 6 months after kidney transplantation, and follow-up period: subsequent 1-5 years.

Measurements

1) Patient background

Patient initials, gender, date of birth, medical chart number · ID number, primary disease, weight, duration of disease, past history, complication(s), date of kidney transplantation, date of hospital discharge, presence or absence of an administration history of Simulect and mouse-derived antibody preparations, presence or absence of human anti-mouse antibodies (HAMA) and human anti-chimeric antibodies (HACA), presence or absence and period of dialysis before the transplantation, kidney transplant type, donor gender, donor age, donor-recipient relationship, number of HLA mismatches, blood type, and donor anti-HLA antibodies.

2) Administration status of the drug

Daily dosage and administration date

3) Blood concentration of the drug

Presence or absence of measured blood concentration of the drug, date of serum collection, and blood concentration of the drug (If blood collection is performed in 10 days, 3 weeks, and 4 weeks after the transplantation, please fill in the date of serum collection and the blood concentration of Simulect)

4) Other treatment situations

Combination drugs (drug names, administration routes, dosages, administration periods, and use reasons)

5) Clinical course

1. Clinical symptoms: The levels of blood pressure, serum creatinine, and BUN from the initiation date of administration of the drug to 6 months later after the transplantation are measured. During follow-up period they should be observed in 1, 2, 3, 4, and 5 years after the transplantation.

2. Rejection: Presence or absence of rejection within 6 months after the completion of the transplantation, types of rejection, date of rejection occurrence, treatment methods, severity, presence or absence of confirmation by biopsy, outcome and date of outcome are observed. During follow-up period they should be observed in 1, 2, 3, 4, and 5 years after the transplantation.

6) Kidney transplant

Presence or absence of kidney transplant engraftment 6 months after the transplantation:

During followed-up period it should be observed in 1, 2, 3, 4, and 5 years after the transplantation.

7) Adverse events

8) Discontinuation · Dropout

If the second administration of the drug is not performed, you should enter the date and reason(s) in the section of discontinuation·dropout.

Study population /Sample size

76 renal transplant patients who received Simulect 10 mg for pediatric intravenous injection.

Outcomes/endpoints/Statistical Methods

Safety assessments

1) Occurrence of adverse reaction and infection

2) Possible element which affects safety (sex, age, body weight, concomitant disease, previous disease, pre-transplantation dialysis and duration of dialysis, allograft type, sex of donor, age of donor, relation between receipient and donor, HLA type mismatch, ABO imcompatible, Immunosuppressant of introduction phase, etc.)

3) Adverse event occurred during or post treatment

Appropriate statistical methods (t-test multiple comparison, x2-test, H-test, U-test, Kaplan Meier method, Log-Rank test etc.) should be used according to the type of data.

Efficacy assessments

Possible element which affects efficacy (sex, age, body weight, concomitant disease, previous disease, pre-transplantation dialysis and duration of dialysis, allograft type, sex of donor, age of donor, relation between receipient and donor, HLA type mismatch, ABO incompatibility, Immunosuppressant of introduction phase, etc.)

Survival rate

Appropriate statistical methods (t-test multiple comparison, x2-test, H-test, U-test, Kaplan Meier method, Log-Rank test etc.) should be used according to the type of data.

Results

Recruitment/ Number analysed

of planned subjects: All renal transplant patients who will receive Simulect 10 mg for

pediatric intravenous injection or were proved to have received the drug.

# of subjects registrated: 80

# of subjects for safety analysis: 76

# of subjects for efficacy analysis: 76

Baseline data

Efficacy results

Of the 76 efficacy analysis subjects, 9 patients experienced 11 graft rejections within 6 months of transplantation, and the incidence of rejection was 11.84% (9/76 patients).

For the efficacy followup, survival rates and graft survival rates at Month 6, Year 1, Year 2, and Year 3 were 100.00% in all of them. The incidence without rejection was 88.00% at Month 6, 83.37% at Year 1, 77.42% at Year 2, and 55.30% at Year 3.

There was no patient background factor that influences presence or absence of graft rejection.

Graft rejection was noted in 1 patient of special patient population (surveillance sheets collected only in patients with hepatic function disorder) and resolved. Graft loss of transplanted kidney and death did not occur.

Safety results

A total of 30 adverse drug reactions were reported in 12 patients of the 76 safety analysis subjects. The incidence of adverse drug reaction was 15.79% (12/76 patients).

The preferred term and incidence of adverse drug reactions noted in ≥ 2 patients were: cytomegalovirus viraemia in 7.89% (6/76 patients), bronchitis in 5.26% (4/76 patients), hypertension in 3.95% (3/76 patients), cytomegalovirus infection, blood pressure decreased, oral herpes, and cardiac failure in 2.63% (2/76 patients).

″ Complication″ was mentioned earlier as a patient background factor that influences the onset of adverse drug reactions. However, the complications experienced in patients who developed adverse drug reaction were also experienced by patients who did not develop adverse drug reaction, and the detail of complications did not differ significantly in the both groups: thus, there was no specific complication that deemed to influence onset of adverse drug reaction.

No adverse drug reaction was noted in special patient population (patients with body weight < 10 kg, patients with hepatic function disorder).

No patient developed hypersensitivity that was an intensive investigation item.

Two cases of secondary malignancy developed in two patients and were both post-transplant lymphoproliferative disorders. Secondary malignancy developed 5 months after the transplantation in one patient and resolved. Its causal relationship between the malignancy and all immunosuppressants including Simulect was not ruled out. Secondary malignancy developed 7 months after the

transplantation in another patient and resolved. Its causal relationship between malignancy and Simulect was ruled out.

Study CCHI621AJP01

Description

PMS study CCHI621AJP01 included a total of 1559 kidney transplant patients. One hundred and seven (107) patients were paediatric patients. Their mean age (±SD) was 8.2±4.1 years (range 1-14). Among the paediatric patients, 91 had a body weight of less than 35 kg and 16 had a body weight of 35 kg or more.

Of the 91 paediatric patients with body weight of less than 35 kg, 74 received 2 doses of 10 mg Simulect. A total of 13 patients received 2 doses of 20 mg Simulect, 1 patient received 1 dose of 20 mg Simulect because 10 mg formulation was unavailable, and 3 patients received 1 dose of 10 mg. Of the 3 patients who received 1 dose of 10 mg Simulect, two did not receive the second dose due to AEs and had rejection episode, and the remaining patient had a body weight of less than 10 kg (8.6 kg). Of 16 paediatric patients with body weight ≥ 35

Methods

Objectives

Study design

Study population /Sample size

A total of 107 pediatric patients were enrolled into the survey: 6-month survey sheets were collected from 107 patients, 1-year survey sheets were collected from 46 patients, 2-year survey sheets were collected from 44 patients, 3-year survey sheets were collected from 42 patients, 4-year survey sheets were collected from 39 patients, and 5-year survey sheets were collected from 37 patients.

Of the 107 pediatric patients, there were 91 patients with body weights < 35 kg: 6-month survey sheets were collected from 91 patients, 1-year survey sheets were collected from 41 patients, 2-year survey sheets were collected from 39 patients, 3-year survey sheets were collected from 37 patients, 4-year survey sheets were collected from 35 patients, and 5-year survey sheets were collected from 33 patients. There were 16 patients with body weights ≥ 35 kg: 6-month survey sheets were collected from 16 patients, 1-year survey sheets were collected from 5 patients, 2-year survey sheets were collected from 5 patients, 3-year survey sheets were collected from 5 patients, 4-year survey sheets were collected from 4 patients, and 5-year survey sheets were collected from 4 patients.

Of 91 pediatric patients with body weight < 35 kg, there were 74 patients who received 2 doses of 10 mg Simulect, being the highest. A total of 13 patients received 2 doses of 20 mg Simulect, 1 patient received 1 dose of 20 mg Simulect because 10 mg formulation was unavailable, and 3 patients received 1 dose of 10 mg. Of the 3 patients who received 1 dose of 10 mg Simulect, 2 patients had rejection of their transplanted kidneys due to AEs and did not receive the second dose, and the remaining 1 patient had body weight less than 10 kg (8.6 kg). Of 16 pediatric patients with body weight ≥ 35 kg, there were 14 patients who received 2 doses of 20mg Simulect, and 2 patients received 2 doses of 10 mg Simulect (Table A-10).

Table A-10 Number of patients by dose

	Children with body weight < 35 kg				Children with body weight ≥ 35 kg				Total
	10 mg × 1 dose	10 mg × 2 doses	20 mg × 1 dose	20 mg × 2 doses	10 mg × 1 dose	10 mg × 2 doses	20 mg × 1 dose	20 mg × 2 doses	
Number of patients collected	3	74	1	13	0	2	0	14	107

The safety analysis set of the pediatric patients included 105 of 107 patients enrolled into the survey after excluding 2 patients who started the treatment before the contract was concluded

Results

Recruitment/ Number analysed

PMS study CCHI621AJP01 included a total of 1559 kidney transplant patients. One hundred and seven (107) patients were paediatric patients. Their mean age (±SD) was 8.2±4.1 years (range 1-14). Among the paediatric patients, 91 had a body weight of less than 35 kg and 16 had a body weight of 35 kg or more.

Baseline data

Patient characteristics by patterns of Simulect administration (pediatric patients)

Factors and stratifications			Patterns of administration				Total
			10 mg × 1 dose	10 mg × 2 doses	20 mg × 1 dose	20 mg × 2 doses	
Total	Total		3	75	1	26	105
Sex (patient)	Male		1 (33.33%)	41 (54.67%)	1 (100.00%)	17 (65.38%)	60 (57.14%)
	Female		2 (66.67%)	34 (45.33%)	0 (0.00%)	9 (34.62%)	45 (42.86%)
Age (yr) (patient)	Mean ± SD		5.67 ± 4.51	7.12 ± 3.76	7 ±	11.7 ± 2.74	8.2 ± 4.1
	Median		6	7	7	13	8
	min. - max.		1 - 10	2 - 14	7 - 7	4 - 14	1 - 14
Body weight (kg)	Mean ± SD		16 ± 7.45	18.5 ± 6.76	19 ±	33.5 ± 10.2	22 ± 10
	Median		15.8	17	19	34.5	19
	min. - max.		8.6 - 23.5	9.3 - 37	19 - 19	12.2 - 53	8.6 - 53
Primary disease	Glomerulonephritis chronic		0	7	0	4	11
	Pyelonephritis		0	0	0	0	0
	Cystic kidney		0	5	0	0	5
	Purpura nephritis		0	0	0	0	0
	SLE (Lupus nephritis)		0	0	0	2	2
	Nephrosclerosis		0	0	0	0	0
	Focal glomerulosclerosis		0	6	0	2	8
	Diabetic nephropathy		0	0	0	0	0
	Others		3	57	1	18	79
Complication	Yes		1 (33.33%)	20 (26.67%)	1 (100.00%)	11 (42.31%)	33 (31.43%)
	Major complication	Hepatic function disorder	0 (0.00%)	1 (1.33%)	0 (0.00%)	0 (0.00%)	1 (0.95%)
History of dialysis	Duration of dialysis (mo)	Mean ± SD	38.3 ± 24.4	34.9 ± 24.8	24 ±	31.8 ± 28.5	34 ± 25
		Median	29	30.5	24	27	30
		min. - max.	20 - 66	2 - 106	24 - 24	6 - 124	2 - 124
	Yes/No	No	0	12	0	10	22
		Yes	3	63	1	16	83
Information on organ donnor	Age (yr)	Mean ± SD	37.3 ± 3.21	39.6 ± 8.87	33 ±	44 ± 9.33	41 ± 9
		Median	36	37	33	42	39
		min. - max.	35 - 41	20 - 72	33 - 33	29 - 65	20 - 72
	Sex	Male	1	37	1	10	49
		Female	2	37	0	15	54
		Unknown/not recorded	0	1	0	1	2

Efficacy results

Rejection Episodes

The rate of rejection episodes in children at 6 months after transplantation was 11.43% (12/105 patients), as compared to 21.2% (307/1445) in adults. The graft survival rate was 93.33% (98/105 patients), and no other significant difference was noted between children and adults.

The rejection rate was 7.78% (7/90 patients) in children with body weight < 35 kg and their graft survival rate was 92.22% (83/90 patients). No other difference was noted between children with body weight < 35 kg and other patients.

A separate evaluation included three patients with body weight < 10 kg, whose ages were 3 years, 2 years and 1 year.

The 3-year old and 2-year old had no ADR and no rejection episode. The 1-year-old patient (body weight of 8.6 kg) developed renal vein thrombosis on the day of transplantation after receiving the initial dose of Simulect 10 mg. The patient experienced graft function failure of the transplanted kidney on Day 8 post-transplantation, and did not receive the second dose of Simulect. The causal relationship of Simulect to renal vein thrombosis was determined to be ruled out.

Proportion of rejection at 6 months between children and adults

Factor and stratification		Number of patients	Rejection		Proportion of rejection	Analytical test results
			No	Yes		
Total		1550	1231	319	20.58%	
Children / Aduts	Age < 15 yrs	105	93	12	11.43%	Fisher p=0.0169
	Age ≥ 15 yrs	1445	1138	307	21.25%	

Graft survival rate at 6 months between children and adults

Factor and stratification		Number of patients	Graft survival		Graft survival rate	Analytical test results
			No	Yes		
Total		1549	58	1491	96.26%	
Children / Adults	Age < 15 yrs	105	7	98	93.33%	Fisher p=0.1080
	Age ≥ 15 yrs	1444	51	1393	96.47%	

Safety results

A total of 26 ADRs were reported in 19 patients in the safety analysis set of 105 children. The most frequent ADRs were cytomegalovirus infection in 11.43% (12/105 patient), hypertension in 2.86% (3/105 patients), and urinary tract infection in 1.90% (2/105 patients).

These ADRs were also found in adult patients with an incidence of 9.13% (132/1446 patients) for cytomegalovirus infection, 1.18% (17/1446 patients) for hypertension, and 0.55% (8/1446 patients) for urinary tract infection. In conclusion these ADRs were not considered to be characteristic to pediatric patients.

A total of 14 serious ADRs were reported in 9 of 105 paediatric patients. The incidence of serious ADRs was 8.57% (9/105 patients), being lower than that of 13.07% (189/1446 patients) in adult patients. Serious ADRs were cytomegalovirus infection in 4.76% (5/105 patients), hypertension in 1.90% (2/105 patients), BK virus infection, upper respiratory tract inflammation, fungal peritonitis, renal vein thrombosis, pyelonephritis, urinary tract infection, and cystitis in 0.95% (1/105 patients) each. Outcome of these serious ADRs in 9 paediatric patients were full recovery in 3 patients, ongoing recovery in 4 patients, absence of recovery in 1 patient and death in 1 patient whose serious ADR was fungal peritonitis. Serious cytomegalovirus infection and serious hypertension were also found in adult patients with an incidence of 5.26% (76/1446 patients) and 0.07% (1/1446 patients), respectively. These serious ADRs were not considered to be characteristic to paediatric patients. Serious ADRs were reported separately and diligently to Novartis safety database and to Health Authorities in compliance to Pharmacovigilance regulations.

One case of Epstein-Barr virus associated lymphoproliferative disorder was reported in a 15- year old patient.

The incidence of ADRs was no different in patients with a body weight of less than < 35 kg (18.89%; 17/90) as compared to those with body weight ≥ 35kg (24.38%; 355/1456).

Proportion of patients with ADR between children and adults

Factor and stratification		Number of patients	Onset of ADR		Patients w/ ADR (%)	Analytical test results
			No	Yes		
Total		1551	1179	372	23.98%	
Children / Adults	Age< 15 yrs	105	86	19	18.10%	Fisher p=0.1565
	Age ≥ 15 yrs	1446	1093	353	24.41%	

2.3.3. Discussion on clinical aspects

In summary, the design, nature of data collection and extensiveness of data reporting in Japanese PMS are limited as compared to what would be expected from a clinical trial. The data presented are difficult to interpret as the no study reports in English are available. Nevertheless, no unexpected findings were recorded neither with regard to efficacy of safety. Efficacy appears to be maintained ore even better (rejection episodes appeared to be less frequent than in adults) and the adverse events recorded were expected considering the known safety profile of Simulect. Data were obtained during the 6-month to 5-year period following kidney transplantation in a total of 187 Japanese pediatric patients who for most of them received two doses of 10 mg Simulect. CMV infections were the most frequent events. Lymphoproliferative disorders occurred in three patients. Results were similar in patients whose body weight was <35 kg.

3. CHMP's overall conclusion and recommendation

The study reports for studies CCHI621A1401, CCHI621AJP01 is taken note of. Both efficacy and safety data as collected were consistent with previous paediatric data recorded for Simulect. Benefit/risk remains unchanged.

These data do not modify the benefit/risk assessment of Simulect in paediatric subjects

☒ **Fulfilled:**

No regulatory action required.