Sponsor

Novartis Pharma

Generic Drug Name

Basiliximab

Therapeutic Area of Trial

Renal transplantation

Approved Indication

Indicated for the prevention of acute rejection after renal transplantation

Protocol Number

CCHI621AFR05

Title

Prospective, multicenter, randomized, open-label, phase 2, lasting 12 weeks, evaluating the pharmacodynamics, efficacy and safety of basiliximab in de novo adult renal transplant patients at low risk receiving either a cumulative dose of basiliximab of 40 or 80 mg in combination with cyclosporine microemulsion, or a cumulative dose of 80 mg of basiliximab without calcineurin inhibitor, with additional follow-up of 12 weeks.

Study Phase

Phase II

Study Start/End Dates

08 Mar 2012 to 21 Mar 13

Study Design/Methodology

Proof of concept, phase 2, national, prospective, multicenter, randomized, open label study with 3 parallel treatment arms designed to evaluate the pharmacodynamics of 2 cumulative doses of Simulect® (either 40 mg or 80 mg) associated or not with a CNI, for 12 weeks post

transplantation. An additional 12 weeks follow-up (until 24 weeks post transplantation) was set up to evaluate long-term safety and tolerability of Simulect®.
Prior to transplantation and first Simulect® injection, eligible patients were randomized in a 1:2:2 ratio in one of the 3 following parallel arms:

- Arm 1 (control): Simulect® 40 mg + Neoral® + Myfortic® + corticosteroids.
- Arm 2: Simulect® 80 mg + Neoral® + Myfortic® + corticosteroids.
- Arm 3: Simulect® 80 mg + Certican® + Myfortic® + corticosteroids.

Centers

3 centers in France

Objectives

Primary objective: to describe and to compare the saturation kinetics of the IL-2R α chain (CD25 antigen) by Simulect® at 12 weeks post transplantation in adult low risk *de novo* renal transplant recipients, receiving either a cumulative dose of 40 or 80 mg of Simulect® in association with Neoral® or a cumulative dose of 80 mg of Simulect® with immunosuppressant therapy that did not include a calcineurin inhibitor (CNI).

Secondary objectives: to describe and to evaluate the following parameters within and between each arm of patients:
Pharmacodynamics (PD) / pharmacokinetics (PK) between D0 and W12 (or D84) post transplantation

- Binding of basiliximab to CD25 receptors.
- Expression of CD25 receptors on T-lymphocytes.
- Cell count of lymphocyte sub-populations.

Efficacy

- Biopsy proven acute rejection (BPAR) at 12 and 24 weeks post transplantation.
- Treatment failure (BPAR, graft loss, death or loss to follow-up) at 12 and 24 weeks post transplantation.
- Renal function at 24 weeks post transplantation.

Test Product (s), Dose(s), and Mode(s) of Administration

Simulect®
Cumulative dose of 40 mg or 80 mg administered intravenously at D0 (within the 2 hours before transplantation) and D4 post transplantation.

Neoral®
Soft capsules administered orally twice a day at a 12-hour interval at the same time as the other oral immunosuppressant treatments. Initiation within 12 hours post transplantation at a dose of 6–8 mg/kg/day in association with Myfortic®, then adjustment according to blood concentration (D3–W12: 150–220 ng/mL (190 ng/mL) / W12–W24: 120–180 ng/mL (160 ng/mL)

Certican®
Tablets administered orally twice a day at a 12-hour interval at the same time as the other oral immunosuppressant treatments. Initiation within 24 hours post transplantation at an initial dose of 6 mg/day, then adjustment according to trough blood concentration ($6 \leq C_0 \leq 10$ ng/mL)

Statistical Methods

Statistical analyses were performed with SAS® version 9.3.
Following premature end of recruitment, only 16 patients have been included in the study. Due to this low number of patients, only results of descriptive analyses have been retained. Statistical tests and confidence intervals were performed in an exploratory manner. Principal analysis planned at 3 month post-transplantation was removed. Only one final data analysis was performed at 6 month post-transplantation and comprised assessment of criteria planned at 3 and 6 month post-transplantation.

The safety population consisted of all randomized patients having received at least one basiliximab injection, having been transplanted and for whom at least one safety assessment was available after treatment initiation. This population was the reference population for the safety analyses. Intent to treat (ITT) population consisted of all randomized patients having received at least one basiliximab injection and who had been transplanted. This population was the reference population for the efficacy analyses. Per Protocol (PP) population consisted of patients included in the ITT population who have completed the study without protocol deviation excluding from the PP population. PK/PD population consisted of patients included in the ITT population for whom at least one blood sample for PK/PD analyses was collected. This population was the reference population for the PK and PD analyses. PP PK/PD population consisted of patients included in the PP population for whom at least one blood sample for PK/PD analyses was collected.

Descriptive statistics consisted of mean, standard deviation, minimum, maximum and median for quantitative variables and of frequency tables for qualitative variables by visits and treatment arms.

Descriptive statistics were used to analyze demographic characteristics, medical history, serology test results, transplantation and donor characteristics for patients included in the ITT population.

Cumulative dose (mg), dose by injection and time of injection have been described for basiliximab. Exposure duration for everolimus and cyclosporine microemulsion has been described and the C_0 analyzed as continuous and discrete variables versus target values. Analyses were performed by study treatment for the ITT population.
Frequency and duration of temporary treatment discontinuations were analyzed globally and by reason for discontinuation with special attention in case of safety reasons. Analyses were performed by study treatment for the ITT population.
For mycophenolate sodium (concomitant medication), exposure duration, posology, frequency and duration of temporary discontinuations, dose adjustments as well as reasons for dose adjustment have been described by study treatment for the ITT population.
Posology and exposure duration of corticosteroids, frequency of other immunosuppressive treatments and others significant concomitant treatment have been described by treatment arm for the ITT population.

All PD and PK analyses were performed on the PK/PD and PP PK/PD populations.

Main criterion
The primary objective was to describe and compare the saturation of the IL-2R α chain (CD25 antigen) depending on the cumulative dose of Simulect® received (40 or 80 mg) and on its administration in association or not with Neoral®. Saturation was expressed as a percentage of T-lymphocyte expressing CD25 measured at protocol-specified time points using an antibody (basiliximab coupled with a fluorochrome) raised against the binding site of basiliximab. From these measurements, saturation kinetics as well as AUC between D0 and W12 (D84) were estimated in each arm.
The objective was to demonstrate a similar saturation between arm 1 (control) and arm 2 on one hand and between arm 1 and arm 3 on the other hand. Because the 2 comparisons were done simultaneously, performing them with a 0.05 significance threshold ensured a global α risk of 0.05. However, if one of the two equivalences was not demonstrated at the 0.05 significance threshold, the other should be demonstrated with a 0.025 significance threshold.
The primary criterion was the AUC between D0 and D84 (W12). The equivalence testing was to be based upon a margin of 20% corresponding to a difference of 2.4 weeks. AUC with their 95% CI were to be described along with the difference $AUC_{arm\ 2}$ - $AUC_{arm\ 1}$ and $AUC_{arm\ 3}$ - $AUC_{arm\ 1}$ and their 95% CI. Saturation AUC for arm 2 (or arm 3) was to be considered as equivalent to the one for arm 1 if the 95% CI of $AUC_{arm\ 2}$ - $AUC_{arm\ 1}$ (respectively $AUC_{arm\ 3}$ - $AUC_{arm\ 1}$) was included in the equivalence interval [-2.4 weeks, 2.4 weeks] for both the PK/PD and the PP PK/PD populations.
However, statistical tests and confidence intervals were finally performed in an exploratory manner.

Other PK/PD criteria
The following variables were assessed within and between each study arm between D0 and D84 (W12) post transplantation:

- Basiliximab binding to CD25 receptors (AUC and %).
- Cell counts of T, B and NK lymphocytes sub-populations (CD3, CD4, CD8, CD19 and CD56 at D 0, 6, 42 and 84) (10^9/L and proportion of the total number of T cells).

Efficacy assessment

The following criteria were described overall and by study treatment for the ITT population.

- Frequency, type (cellular or antibody mediated), severity (Banff grade) of BPAR at 12 and 24 weeks.
- Frequency of treatment failure (composite criteria including BPAR, death, graft loss and loss to follow-up) at 12 and 24 weeks.
- Renal function as assessed by creatinemia, estimated Glomerular Filtration Rate, [abbreviated modification of diet in renal disease (MDRDa) formula]. A secondary analysis using the last observation carried forward (LOCF) method in case of missing data was performed. Analyses were performed with baseline value as D8.

Safety assessment

Number and frequency of patients having experienced at least one event was presented by study arms. Frequency of AEs, especially infection and cancer, was provided by system organ classes (SOC), preferred term (PT) and by period during which the event occurred for each study arm. Information regarding severity and relation to treatment (for Simulect®, Neoral® and Certican®) were described. Detailed description of SAEs and events leading to premature treatment discontinuation was also provided.

Descriptive statistics for weight, blood pressure and laboratory safety tests and their evaluation over time are described in the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female patients aged between 18 and 65 years
- Patients receiving a primary renal graft from a deceased or living, related or unrelated donor and who require Simulect® induction therapy
- Cold ischemia time < 30 hours

Exclusion criteria

- Patients undergoing multi-organ transplantation, including both kidneys, or who have previously undergone organ transplantation, including renal transplantation
- Patients receiving a graft from a non-heart-beating donor
- A-B-O incompatible graft or positive T cell crossmatch
- Patients receiving a graft from an expanded criteria donor according to the UNOS definition (donor older than 60 years or donor aged between 50 and 60 years and presence of at least 2 of the following factors: hypertension, serum creatinine concentration ≥ 132 µmol/mL, cardiovascular cause of death)
- Positive anti-HLA antibodies (Luminex) prior to transplantation
- Patients whose original renal disease was primary focal and segmental hyalinosis or was related to atypical hemolytic uremic syndrome
- EBV-negative patients receiving a graft from an EBV-positive donor (EBV D+R-)

Other protocol-defined inclusion/exclusion criteria applied

Participant Flow

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids	Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids	Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	Total
Started	3	6	7	16
Completed	2	6	4	12
Not Completed	1	0	3	4
	Reason for Not Completed			
Total	1	0	3	4
Adverse Event	1	0	2	3
Lack of Efficacy	0	0	1	1

Baseline Characteristics

Overall Number of Baseline Participants

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids	Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids	Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	Total
Overall Number of Baseline Participants	3	6	7	16

Age Continuous (years)
Standard Deviation
Mean

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids	Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids	Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	Total
age	53.7 (8.7)	45.0 (11.4)	39.7 (12.2)	44.3 (11.9)

	Gender, Male/Female (participants) Number			
	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids	**Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**	**Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**	**Total**
Female	0	2	2	4
Male	3	4	5	12

Outcome Measures

Summary of Efficacy

Primary Outcomes Result(s)

1. **Saturation kinetics (Area under the curve (AUC)) of CD25 antigen by basiliximab**. CD25 saturation is the percentage of T cells expressing CD25. AUC was calculated between the first injection of basiliximab (D0) and D84 only for patients who received two Simulect® injections: PK/PD population.

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		**Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**		**Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**	
Number of Participants Analyzed:	3		6		6	
Saturation kinetics (Area under the curve (AUC)) of CD25 antigen by basiliximab Units: weeks	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
	8.4	1.61	11.1	1.12	9.7	0.70

2. **Saturation rate of CD25 antigen saturation by basiliximab**. CD25 saturation is the percentage of T cells expressing CD25 at D0, D1, D4, D6, D14, D21, D28, D42, D56 and D84 (W12) post-transplantation: PK/PD population.

Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0	**Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0**	**Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0**

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids		Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	
Number of Participants Analyzed:	3		6		7	
Saturation rate of CD25 antigen saturation by basiliximab Units: Percentage	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
Day 0 (D0) (before injection)	0.0	0.00	0.0	0.00	0.0	0.00
D0 (2 hours after injection)	93.7	10.97	96.7	8.16	94.7	5.19
D1	95.7	7.51	97.7	5.24	99.0	2.65
D4 (before injection): (3, 6, 6)	100.0	0.00	96.2	6.88	93.7	9.89
D4 (2 hours after injection): (3, 6, 5)	96.7	5.77	96.3	6.83	84.8	19.25
D6: (3, 6, 6)	98.7	2.31	100.0	0.00	94.0	14.70
D14: (3, 6, 6)	98.3	2.89	96.7	7.23	97.3	6.53
D21: (3, 6, 6)	100.0	0.00	94.5	10.80	92.5	11.83
D28: (3, 6, 6)	95.3	4.16	100.0	0.00	92.7	9.33
D42: (3, 6, 5)	78.3	9.07	100.0	0.00	99.2	1.79
D56: (3, 6, 5)	65.0	56.35	93.3	13.20	94.2	12.97
D84 (Week 12): (3, 6, 5)	0.0	0.00	67.5	48.55	14.2	20.86

Secondary Outcome Result(s)

1. **AUC of basiliximab binding to CD25 receptors**. AUC was calculated between the first injection of basiliximab (D0) and D84 only for patients who received two Simulect® injections: PK/PD population.

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids		Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	
Number of Participants Analyzed:	3		6		6	
AUC of basiliximab binding to CD25	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**

receptors Units: weeks						
	7.0	1.80	9.9	2.22	8.4	0.75

2. **Rate of basiliximab binding to CD25 receptors**. This is the percentage of T cells binding basiliximab at D0, D1, D4, D6, D14, D21, D28, D42, D56 and D84 (W12) post-transplantation: PK/PD population.

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids		Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	
Number of Participants Analyzed:	3		6		7	
Rate of basiliximab binding to CD25 receptors Units: Percentage	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
D0 (before injection)	0.0	0.00	0.0	0.00	4.7	12.47
D0 (2 hours after injection)	95.3	8.08	96.2	9.39	81.6	28.30
D1 (n: 3, 5, 7)	70.0	28.58	64.8	35.15	91.4	11.65
D4 (before injection): (n: 3, 6, 6)	100.0	0.00	59.0	45.98	53.0	33.33
D4 (2 hours after injection): (n: 3, 5, 5)	100.0	0.00	83.4	20.14	81.2	16.02
D6: (n: 3, 6, 6)	91.7	14.43	99.0	2.45	98.3	4.08
D14: (n: 3, 6, 6)	100.0	0.00	89.0	22.00	93.8	15.11
D21: (n: 3, 6, 6)	89.0	19.05	87.7	26.93	85.8	32.31
D28: (n: 3, 6, 6)	76.3	17.62	91.0	14.00	82.7	26.29
D42: (n: 3, 6, 5)	47.3	28.22	84.0	19.75	78.8	30.11
D56: (n: 3, 6, 5)	53.0	41.80	88.8	27.35	75.2	15.29
D84 (W12): (n: 3, 6, 5)	6.7	6.11	57.7	43.83	15.8	9.73

3. **Proportion of CD3+, CD4+, CD8+, CD19+ and CD56+ T cells**. Cell counts of various subpopulations of T, B and NK lymphocytes (CD3, CD4, CD8, CD19 and CD56) (flow cytometry) at D0, D6, D42, D84 (Wk12) post-transplantation: PK/PD population.

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids		Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	
Number of Participants Analyzed:	3		6		7	
Proportion of CD3+, CD4+, CD8+, CD19+ and CD56+ T cells Units: 10^9/L	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
CD3 cells count at D0 (before injection)	0.5	0.25	0.9	0.28	0.7	0.28
CD3 cells count at D6: (n: 3, 6, 6)	0.6	0.39	1.1	0.50	0.9	0.75
CD3 cells count at D42: (n: 3, 6, 5)	0.5	0.09	1.2	0.96	1.1	1.18
CD3 cells count at D84 (W12): (n: 3, 6, 6)	0.8	0.58	1.2	0.72	1.1	1.22
CD4 cells count at D0 (before injection)	0.4	0.19	0.6	0.20	0.5	0.22
CD4 cells count at D6:0.5 (n: 3, 6, 6)	0.5	0.30	0.7	0.28	0.6	0.59
CD4 cells count at D42: (n: 3, 6, 5)	0.3	0.08	0.8	0.53	0.8	0.82
CD4 cells count at D84 (W12): (n: 3, 6, 6)	0.6	0.36	0.8	0.42	0.7	0.86
CD8 cells count at D0 (before injection)	0.1	0.05	0.3	0.13	0.2	0.15
CD8 cells count at D6: (n: 3, 6, 6)	0.2	0.08	0.3	0.25	0.2	0.24
CD8 cells count at D42: (n: 3, 6, 5)	0.1	0.05	0.3	0.44	0.4	0.37
CD8 cells count at D84 (W12): (n: 3, 6, 6)	0.2	0.24	0.3	0.32	0.3	0.37
CD19 cells count at D0 (before injection)	0.1	0.08	0.1	0.10	0.1	0.05

CD19 cells count at D6: (n: 3, 6, 6)	0.1	0.07	0.2	0.27	0.2	0.17
CD19 cells count at D42: (n: 3, 6, 5)	0.1	0.09	0.2	0.21	0.2	0.18
CD19 cells count at D84 (W12): (n: 3, 6, 6)	0.2	0.20	0.1	0.11	0.1	0.15
CD56 cells count at D0 (before injection)	0.1	0.20	0.2	0.14	0.2	0.31
CD56 cells count at D6: (n: 3, 6, 6)	0.1	0.00	0.1	0.06	0.2	0.25
CD56 cells count at D42: (n: 3, 6, 5)	0.1	0.05	0.2	0.10	0.2	0.13
CD56 cells count at D84 (W12): (n: 3, 6, 6)	0.1	0.05	0.1	0.03	0.1	0.15

4. **Incidence of Biopsy Proven Acute Rejection (BPAR)** at D84 (W12) and W24 post-transplantation: ITT population.

	Arm 1 **A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids**	**Arm 2** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**	**Arm 3** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**
Number of Participants Analyzed:	3	6	7
Incidence of Biopsy proven acute rejection (BPAR) **Units: percentage**	**Number**	**Number**	**Number**
D84 (W12): No	66.7	83.3	42.9
D84 (W12):Yes	33.3	16.7	57.1
W24: No	66.7	83.3	42.9
W24:Yes	33.3	16.7	57.1

5. **Type and Severity of BPAR** at D84 (W12) and W24 post-transplantation: ITT population.
   Antibody mediated acute rejection: C4d deposition, presence of circulating antidonor antibody, morphologic evidence of acute tissue injury such as acute tubular necrosis-like minimal inflammation or capillary and/or glomerular inflammation and/or thromboses or arterial inflammation.

Cellular acute rejection: acute T-cell mediated rejection
-Type IA: Significant interstitial infiltration (> 25% of parenchyma) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells).
-Type IB: Significant interstitial infiltration (> 25% of parenchyma) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells).
-Type IIA: Mild to moderate intimal arteritis.
-Type IIB: Severe intimal arteritis comprising > 25% of the lumenal area.
-Type III: Transmural (full vessel wall thickness) arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (with accompanying lymphocytic inflammation).

	Arm 1 **A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids**	**Arm 2** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**	**Arm 3** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**
Number of Participants Analyzed:	3	6	7
Type and Severity of BPAR **Units: percentage**	**Number**	**Number**	**Number**
D84 (W12): Antibody mediated AR - No	66.7	100.0	85.7
D84 (W12): Antibody mediated AR - Yes	33.3	0.0	14.3
D84 (W12): Cellular AR - No	100.0	83.3	57.1
D84 (W12): Cellular AR - Yes	0.0	16.7	42.9
D84 (W12): Banff type lA	0.0	0.0	14.3
D84 (W12): Banff type lB	0.0	16.7	14.3
D84 (W12): Banff type llA	0.0	0.0	0.0
D84 (W12): Banff type llB	0.0	0.0	14.3
D84 (W12): Banff type lll	0.0	0.0	0.0
W24: Antibody mediated AR - No	66.7	100.0	85.7
W24: Antibody mediated AR - Yes	33.3	0.0	14.3
W24: Cellular AR - No	100.0	83.3	57.1
W24: Cellular AR - Yes	0.0	16.7	42.9
W24: Banff type lA	0.0	0.0	0.0
W24: Banff type lB	0.0	16.7	28.6
W24: Banff type llA	0.0	0.0	0.0

W24: Banff type llB	0.0	0.0	14.3
W24: Banff type lll	0.0	0.0	0.0

6. **Incidence of treatment failures at D84 (W12) and W24 post-transplantation.** Treatment failure was defined either as a BPAR, a graft loss, a death or a loss to follow-up. An extended treatment failure was also defined including treated borderline lesions, BPAR, graft loss, death or loss to follow-up. Treated borderline lesions were considered as acute rejection: ITT population.

	Arm 1 **A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids**	**Arm 2** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**	**Arm 3** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**
Number of Participants Analyzed:	3	6	7
Incidence of treatment failures **Units: percentage**	**Number**	**Number**	**Number**
D84 (W12): BPAR and/or borderline lesions- No	66.7	66.7	14.3
D84 (W12): BPAR and/or borderline lesions- Yes	33.3	33.3	85.7
D84 (W12): Graft loss - No	66.7	100.0	100.0
D84 (W12): Graft loss - Yes	33.3	0.0	0.0
D84 (W12): Death - No	100.0	100.0	100.0
D84 (W12): Death - Yes	0.0	0.0	0.0
D84 (W12): Loss to follow-up - No	100.0	100.0	100.0
D84 (W12): Loss to follow-up - Yes	0.0	0.0	0.0
W24: BPAR or borderline lesions - No	66.7	66.7	14.3
W24: BPAR or borderline lesions - Yes	33.3	33.3	85.7
W24: Graft loss - No	66.7	100.0	100.0
W24: Graft loss - Yes	33.3	0.0	0.0
W24: Death - No	100.0	100.0	100.0
W24: Death - Yes	0.0	0.0	0.0
W24: Loss to follow-up - No	100.0	100.0	100.0
W24: Loss to follow-up -	0.0	0.0	0.0

Yes

7. **Change from baseline (D8) to W24 in estimated glomerular filtration rate (eGFR)**. (MDRDa formula) with imputation by last observation carried forward (LOCF): ITT population.

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids		Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids		Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	
Number of Participants Analyzed:	3		6		7	
Change from baseline (D8) in estimated glomerular filtration rate (eGFR) Units: mL/min/1.73m^2	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**	**Mean**	**Standard Deviation**
D8	35.0	13.20	53.8	23.79	49.9	18.45
W24 (n: 3, 6, 6)	31.9	27.93	55.7	15.68	54.4	10.48

Summary of Safety

Safety Results

Adverse Events by System Organ Class

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids N (%)	Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids N (%)	Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids N (%)
Patients studied			
Randomized patients	3	6	7
Patients with at least one AE	3 (100.0)	6 (100.0)	7 (100.0)
Patients with drug-related (to Simulect®) AE	0 (0.0)	0 (0.0)	1 (14.3)
AEs by primary system organ class			
Blood and lymphatic system disorders	1 (33.3)	4 (66.7)	2 (28.6)
Gastrointestinal disorders	1 (33.3)	3 (50.0)	4 (57.1)
General disorders and administration site conditions	3 (100.0)	1 (16.7)	3 (42.9)
Hepatobiliary disorders	1 (33.3)	3 (50.0)	0 (0.0)
Immune system disorders	1 (33.3)	0 (0.0)	2 (28.6)

Infections and infestations	0 (0.0)	3 (50.0)	5 (71.4)
Injury, poisoning and procedural complications	2 (66.7)	0 (0.0)	3 (42.9)
Investigations	1 (33.3)	2 (33.3)	2 (28.6)
Metabolism and nutrition disorders	1 (33.3)	3 (50.0)	6 (85.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	3 (50.0)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	2 (28.6)
Renal and urinary disorders	1 (33.3)	0 (0.0)	2 (28.6)
Reproductive system and breast disorders	0 (0.0)	1 (16.7)	1 (14.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (33.3)	1 (14.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (16.7)	1 (14.3)
Vascular disorders	2 (66.7)	1 (16.7)	6 (85.7)

Most Frequently Reported AEs Overall by Preferred Term

	Arm 1 **A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids**	**Arm 2** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids**	**Arm 3** **A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids**	**Total**
Overall number of patients	**3**	**6**	**7**	**16**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Hypertension	2 (66.7%)	1 (16.7%)	4 (57.1%)	7 (43.8%)
Anaemia	1 (33.3%)	2 (33.3%)	2 (28.6%)	5 (31.3%)
Oedema peripheral	3 (100.0%)	1 (16.7%)	1 (14.3%)	5 (31.3%)
Blood creatinine increased	0 (0.0%)	2 (33.3%)	2 (28.6%)	4 (25.0%)
Cytolytic hepatitis	1 (33.3%)	3 (50.0%)	0 (0.0%)	4 (25.0%)
Acidosis	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (12.5%)
Aphthous stomatitis	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (12.5%)
Complications of transplanted kidney	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (12.5%)
Diarrhoea	0 (0.0%)	1 (16.7%)	1 (14.3%)	2 (12.5%)
Gingival hypertrophy	1 (33.3%)	1 (16.7%)	0 (0.0%)	2 (12.5%)
Hypercholesterolaemia	0 (0.0%)	2 (33.3%)	0 (0.0%)	2 (12.5%)
Hyperlipidaemia	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (12.5%)
Hypocalcaemia	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (12.5%)
Hypophosphataemia	0 (0.0%)	1 (16.7%)	1 (14.3%)	2 (12.5%)
Intra-abdominal haematoma	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (12.5%)
Lung disorder	0 (0.0%)	1 (16.7%)	1 (14.3%)	2 (12.5%)
Neutropenia	0 (0.0%)	2 (33.3%)	0 (0.0%)	2 (12.5%)
Renal failure acute	0 (0.0%)	0 (0.0%)	2 (28.6%)	2 (12.5%)
Sinusitis	0 (0.0%)	1 (16.7%)	1 (14.3%)	2 (12.5%)
Transplant rejection	1 (33.3%)	0 (0.0%)	1 (14.3%)	2 (12.5%)
Urinary tract infection	0 (0.0%)	1 (16.7%)	1 (14.3%)	2 (12.5%)

Serious Adverse Events and Deaths

	Arm 1 A cumulative dose of 40 mg of Simulect® (20mg at Day 0 (D0) and 20mg at Day 4 (D4)+ Neoral® + Myfortic® + corticosteroids	Arm 2 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Neoral® + Myfortic® + corticosteroids	Arm 3 A cumulative dose of 80 mg of Simulect® (40mg at D0 and 40mg at D4) + Certican® + Myfortic® + corticosteroids	Total
Overall number of patients	**3**	**6**	**7**	**16**
Patient with at least one SAE N (%)	2 (66.7 %)	2 (33.3 %)	5 (71.4 %)	9 (56.3%)
Patients with drug-related (to Simulect®) SAE N (%)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
SAE(s)	4	4	9	17
Death	0	0	0	0

Other Relevant Findings

No other relevant findings

Date of Clinical Trial Report

16 Dec 2013

Date Inclusion on Novartis Clinical Trial Results Database

18 Mar 2014

Date of Latest Update