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EMA/485288/2020
Human Medicines Division

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

Orencia

abatacept

Procedure no: EMEA/H/C/000701/P46/065

Note

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

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Table of contents

1. Introduction

On 29 July 2020, the MAH submitted a study report for a completed clinical study (study number IM101566) for ORENCIA, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The study enrolled a mixed population of adult and paediatric patients.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study number IM101566, entitled "A Phase II Randomized, Placebo-Controlled, Double-Blind, Parallel Arms with Switchover, Pilot Study to Evaluate the Efficacy and Safety of Intravenous Abatacept in Treatment Resistant Nephrotic Syndrome (Focal Segmental Glomerulosclerosis/ Minimal Change Disease)" is a stand alone study.

The MAH stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for ORENCIA and therefore no further impact on the ORENCIA product information is anticipated.

2.2. Information on the pharmaceutical formulation used in the study

Intravenous abatacept, currently marketed for use in adult and paediatric subjects with RA/pJIA, is a sterile, white, preservative-free, lyophilised powder for "concentrate for solution" IV use. This was the formulation used in Study IM101566.

There is no difference in the way the abatacept dose is prepared for and administered to adult and paediatric/adolescent populations. A silicone-free syringe was used to reconstitute the lyophilised powder and for transfer to the infusion bag/bottle.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study number IM101566, entitled "A Phase II Randomized, Placebo-Controlled, Double-Blind, Parallel Arms with Switchover, Pilot Study to Evaluate the Efficacy and Safety of Intravenous Abatacept in Treatment Resistant Nephrotic Syndrome (Focal Segmental Glomerulosclerosis/ Minimal Change Disease)"

2.3.2. Clinical study

Study IM101566

Description

Study IM101566 was a Phase 2 randomised, double-blind, parallel arms with switchover, placebo-controlled multicentre study to evaluate the efficacy and safety of intravenous abatacept in adult and paediatric patients with treatment resistant nephrotic syndrome (TRNS).

Methods

Objective(s)

Primary Objective:

- Demonstrate improvement in nephrotic range proteinuria to sub-nephrotic range while maintaining renal function following treatment with abatacept compared to placebo.
    - Demonstrate difference in percent of renal responders defined by composite renal index at Day 113.

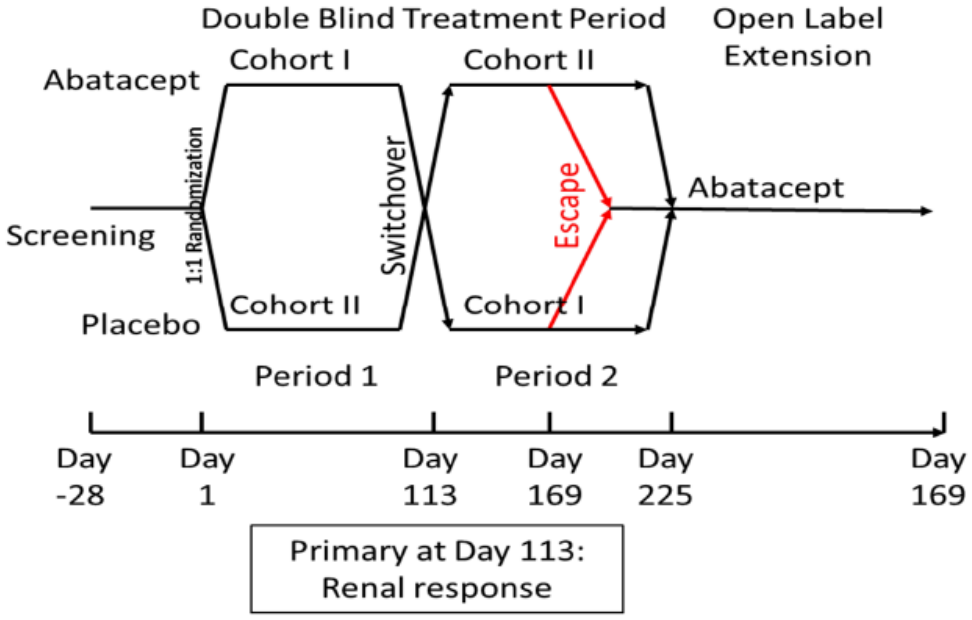
Secondary Objectives:

- Assess improvement in change from baseline in the level of proteinuria following treatment with abatacept compared to placebo.
    - Assess difference in mean change from baseline in urine protein/creatinine ratio (UPCR) at Day 113.
- Assess improvement in serum albumin levels following treatment with abatacept compared to placebo.
    - Assess difference in mean change from baseline in serum albumin at Day 113.
- Assess improvement in complete remission while maintaining renal function following treatment with abatacept compared to placebo.
    - Assess difference in percent of subjects achieving complete remission (UPCR ≤ 0.3) with preservation of eGFR at Day 113.
- Assess improvement in patient reported outcomes related to nephrotic syndrome.
    - Assess changes using the Patient Reported Outcomes Measurement Information System (PROMIS).
- Assess the safety and immunogenicity of abatacept in subjects with TRNS.
    - Describe rates of AEs and SAEs and immunogenicity testing.
- Assess the pharmacokinetics of abatacept in subjects with TRNS.

Study design

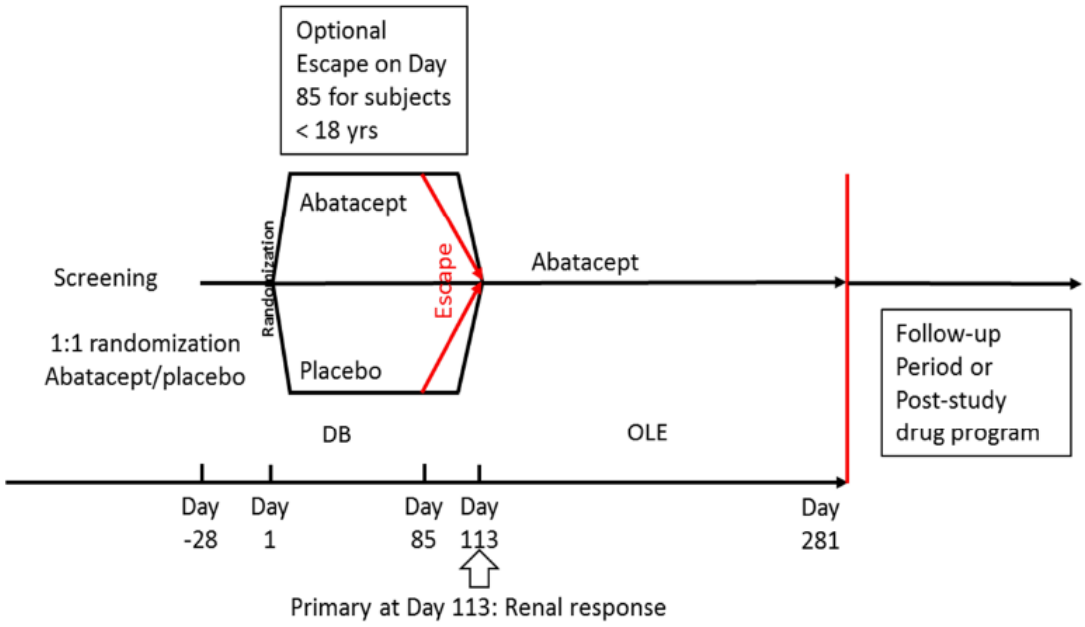
In the original study design, subjects were to be randomised 1:1 to IV abatacept or placebo in a double-blind fashion into parallel arms with a switchover study design. The trial consisted of 5 periods: the Screening Period was 28 days (could be extended an additional 14 days to complete testing by repeating screening labs), a 16 week Treatment Period 1 (parallel arms: IV abatacept vs placebo), a switchover in treatment in a second 16-week Treatment Period 2, and a 169 day abatacept Open Label Extension Period (OLE), and a 6 month Follow-up Period. The original study design is depicted in Figure 1.

Figure 1. Original IM101566 Study Design



In an attempt to improve enrolment, the study design was modified after study initiation within Amendment 2 of the study protocol. The final study design was also to randomise subjects 1:1 to IV abatacept or placebo in a double-blind fashion into parallel arms but without the switchover and a blinded Period 2. The trial consisted of 4 periods: the Screening Period was 28 days (could be extended an additional 14 days to complete testing by repeating screening labs), a 16 week Double-Blind Period (parallel arms: IV abatacept vs placebo), and a 169 day abatacept Open Label Extension Period (OLE), and a 6 month Follow-up Period. An optional early escape for subjects < 18 year of age was available on Day 85. The revised study design is shown in Figure 2.

Figure 2. Revised IM101566 Study Design per Amendment 2



Study population /Sample size

Key inclusion criteria:

- Male and female subjects aged 6 years or older
- Subjects diagnosed with TRNS due to either focal segmental glomerulosclerosis (FSGS) or Minimal Change Disease (MCD) [TRNS (FSGS/MCD)]
    - Pathological findings of either FSGS (excluding collapsing FSGS) or MCD on the most recent renal biopsy (renal biopsies will not be part of this study). This will be confirmed by review of the pathology report (not slides) by a central pathologist
    - UPCR ≥ 3 at screening
    - Treatment resistant defined as:
        - Persistence of UPCR ≥ 3 in spite of therapy with any one of the following agents: corticosteroids (CS), calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus, mycophenolate mofetil (MMF), mycophenolic acid (MPA) or cyclophosphamide
        - Duration of therapy: The duration of CS therapy required to determine treatment resistance will be 6 weeks in subjects < 18 year of age and 12 weeks for subjects ≥ 18 years. For all other agents, the minimum duration of therapy will be 16 weeks, regardless of age
        - Intolerance to any two of these agents, regardless of duration of treatment or age
- Subjects must be receiving either an angiotensin-converting-enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) at stable doses for at least 2 weeks prior to randomisation unless intolerance is documented. Combined use of renin angiotensin system (RAS) inhibitors will not be allowed. If aldosterone inhibitors (spirolactone or eplerenone) or aliskiren (direct renin inhibitor) are used, they must also be at stable doses.
- A minimal level of renal function at screening based on estimated glomerular filtration rate (eGFR) will be required (≥ 45 for both children and adults)
- APOL1 Genotyping. Subjects will be genotyped for the APOL1 renal risk variants SNPs [Risk allele G1 (rs73885319 and rs60910145) and risk allele G2 (rs71785313)]. Subjects with 2 copies of the high-risk APOL1 variants are in the APOL1 high-risk group which will be used for stratification at randomization. Genotyping during screening will not be necessary if results of previous testing are available. Subjects will be allowed to opt-out of genotyping for APOL1. Subjects who refuse genotyping will still be eligible to be randomised.
- Concomitant medication. Subjects may enrol with or without the following background agents used to treat TRNS (FSGS/MCD): CS (low dose, prednisone or equivalent at doses ≤ 10 mg/day), calcineurin inhibitors (cyclosporine and tacrolimus), MMF or MPA. Agents must be used at standard doses, must not have been started within 8 weeks of enrolment and must be stable for at least 4 weeks prior to randomisation. No adjustment in doses of concomitant medications will be allowed during the double-blind period. Dose decrease or holds to address drug-related toxicity are allowed.

Key exclusion criteria:

- Subjects with causes of TRNS other than FSGS or MCD (eg, IgA nephropathy, obesity related glomerulopathy or membranous nephropathy)
- Subjects with collapsing FSGS, also known as collapsing glomerulopathy
- Subjects with systemic lupus erythematosus (SLE)
- Subjects with diabetes mellitus, both type 1 and type 2
- Subjects with clinically significant congestive heart failure (CHF; New York Heart Association [NYHA] Class III or Class IV)
- Body mass index (BMI) > 40 for adults

The study was planned to randomise 90 subjects to assess the primary endpoint of proportion of subjects in Renal Response at Day 113 between the IV Abatacept and placebo arms. Randomisation was stratified by genotype (APOL1 high risk group vs Others) and age (< 18 and ≥ 18 years).

Treatments

Subjects randomised to abatacept treatment in the Double-Blind Period were dosed as follows.

- Adults used the weight-tiered dose: < 60 kg: 500 mg, 60 to 100 kg: 750 mg, > 100 kg: 1000 mg;
- Paediatric patients 6 to 17 years who weigh < 75 kg received 10 mg/kg and those who weigh ≥ 75 kg followed adult dosing.

Dosing was on Day 1, 15, 29 and then every 28 days for 113 days. Subjects in the placebo arm received normal saline or D5W following the same dosing schedule. In the open-label extension, all subjects received age and weight-based IV abatacept every 28 days for 169 days.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects in Renal Response at Day 113. Renal Response was defined as a subject meeting all of the following criteria:

- Proteinuria: Reduction of baseline urine protein/creatinine ratio (UPCR) of ≥ 50% and to less than 3.
- Renal function: No worsening of baseline estimated glomerular filtration rate (eGFR), defined as within normal range if normal at baseline, or ≥ 75% baseline value if below normal at baseline.

Secondary efficacy endpoints included:

- Mean change from baseline in UPCR at Day 113
- Mean change from baseline in serum albumin at Day 113
- Proportion of subjects achieving complete remission (UPCR ≤ 0.3 with eGFR: normal or ≥ 75% of baseline value if below normal at baseline) at Day 113
- Mean change from baseline in PROMIS measures at Day 113.

Safety endpoints included:

- all adverse events (AEs, SAEs, AEs leading to discontinuation, deaths, etc) and AEs of interest (infections, malignancies, autoimmune disorders, infusion related reactions, renal-related events).

The immunogenicity endpoint was the proportion of subjects with positive antibody response relative to baseline over time.

Exploratory endpoints comprised mean change from baseline in serum total cholesterol and triglycerides at Day 113; and mean change in height standard deviation score (HSDS) in subjects < 18 years at Day 113.

Statistical Methods

Table 1 summarises the MAH's planned efficacy analyses.

Table 1. Summary of Planned Efficacy Analyses

Summary of Planned Efficacy Analyses	
Measure of Interest	**Analysis Method**
Renal Response	Primary Analysis: Using a logistic regression model that includes treatment arm, randomization stratification factor (Genotype, Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI and p-value will be provided.
Differences in proportions: proportion of subjects achieving complete remission at Day 113	Secondary Efficacy Analysis: Using a logistic regression model that includes treatment arm, stratification variables (Genotype and Age) and baseline UPCR as continuous variable and point estimate of adjusted ORs, corresponding 95% CI will be provided.
Difference in mean change from baseline in continuous endpoints (UPCR, Serum Albumin, Serum Total Cholesterol, Serum Triglycerides)	Longitudinal (repeated measure) mixed model [including treatment group, baseline value of variable and randomization stratification factors (genotype and Age), time, and time by treatment interaction as fixed effects and subject as a random effect], adjusted mean, SE, 95% CI for adjusted mean difference between treatment groups will be provided.

The primary and secondary efficacy analyses were performed using the ITT Analysis Population by treatment group assigned at randomisation during the double-blind period. The primary analysis was to be repeated using the PP analysis population if more than 10% of subjects in any treatment group met the criteria for a relevant protocol deviation. All other efficacy analyses were performed using the ITT Analysis Population, unless otherwise specified.

Analysis of all safety data followed the MAH's standard safety data conventions and supplements to the standard conventions for the abatacept programs. The evaluation of drug safety was based primarily on clinical AEs, vital signs and laboratory abnormalities reported during the study. All safety presentations were based on the As Treated Analysis Population by treatment group. Unless otherwise specified adverse events and laboratory abnormalities were summarised for double-blind period, cumulative abatacept safety period and OLE period. The efficacy analysis was mainly focused on the double-blind period.

Results

Recruitment/ Number analysed

A total of 66 subjects were enrolled at 24 sites in the US, and 36 were randomised and treated. The remaining 30 enrolled subjects failed to meet study criteria. Of the 36 randomised subjects, 16 were less than 18 years of age.

The enrolment period lasted approximately 36 months. The MAH terminated Study IM101566 prematurely due to concerns over an unexpectedly slow rate of enrolment, in spite of previously extending the study recruitment timelines and multiple efforts to increase enrolment, including a major protocol revision. The Data Monitoring Committee also voiced concern over the slow enrolment to complete and achieve the primary study efficacy assessment and recommended study termination.

Baseline data

For all randomised and treated subjects, the mean (SD) age was 25.8 (16.80) years, 55.6% of subjects were female and most subjects were white (75.0%) and not Hispanic/Latino (80.6%). For the paediatric subjects, mean (SD) age was 11.0 (3.06) years, 43.8% of subjects were female, and most subjects were white (62.5%) and not Hispanic/Latino (75.0%). Baseline demographic characteristics for the entire study population and the paediatric subgroup are summarised in Tables 2 and 3.

Table 2. Summary of Baseline Demographics, All Randomised and Treated Subjects

		ABATACEPT N = 17	PLACEBO N = 19	TOTAL N = 36
AGE (OVERALL) (YEARS)	N	17	19	36
	MEAN	22.5	28.7	25.8
	SD	13.21	19.35	16.80
	MEDIAN	18.0	20.0	19.0
	MIN	6	8	6
	MAX	46	60	60
WEIGHT (KG)	N	17	19	36
	MEAN	71.35	71.29	71.32
	SD	26.524	26.063	25.903
	MEDIAN	65.70	74.00	71.10
	MIN	25.6	24.8	24.8
	MAX	112.9	106.6	112.9
AGE GROUP (YEARS)	<65 YEARS	17 (100.0)	19 (100.0)	36 (100.0)
GENDER (%)	MALE	9 (52.9)	7 (36.8)	16 (44.4)
	FEMALE	8 (47.1)	12 (63.2)	20 (55.6)
RACE (%)	WHITE	13 (76.5)	14 (73.7)	27 (75.0)
	BLACK/AFRICAN AMERICAN	4 (23.5)	3 (15.8)	7 (19.4)
	OTHER	0	2 (10.5)	2 (5.6)
ETHNICITY (%)	HISPANIC/LATINO	2 (11.8)	5 (26.3)	7 (19.4)
	NOT HISPANIC/LATINO	15 (88.2)	14 (73.7)	29 (80.6)

Table 3. Summary of Baseline Demographics, All Randomised and Treated Paediatric Subjects

		ABATACEPT N = 8	PLACEBO N = 8	TOTAL N = 16
AGE (YEARS)	N	8	8	16
	MEAN	11.3	10.8	11.0
	SD	3.85	2.25	3.06
	MEDIAN	11.0	10.5	10.5
	MIN	6	8	6
	MAX	16	15	16
AGE GROUP	< 2 YEARS	0	0	0
	2-5 YEARS	0	0	0
	6-11 YEARS	4 (50.0)	5 (62.5)	9 (56.3)
	12-17 YEARS	4 (50.0)	3 (37.5)	7 (43.8)
WEIGHT (KG)	N	8	8	16
	MEAN	57.74	51.90	54.82
	SD	27.752	23.362	24.964
	MEDIAN	58.65	46.95	55.80
	MIN	25.6	24.8	24.8
	MAX	112.9	90.1	112.9
WEIGHT CATEGORY (%)	< 25 KG	0	1 (12.5)	1 (6.3)
	25-50 KG	3 (37.5)	3 (37.5)	6 (37.5)
	> 50 KG	5 (62.5)	4 (50.0)	9 (56.3)
GENDER (%)	MALE	6 (75.0)	3 (37.5)	9 (56.3)
	FEMALE	2 (25.0)	5 (62.5)	7 (43.8)
RACE (%)	WHITE	4 (50.0)	6 (75.0)	10 (62.5)
	BLACK/AFRICAN AMERICAN	4 (50.0)	1 (12.5)	5 (31.3)
	OTHER	0	1 (12.5)	1 (6.3)
ETHNICITY (%)	HISPANIC/LATINO	1 (12.5)	3 (37.5)	4 (25.0)
	NOT HISPANIC/LATINO	7 (87.5)	5 (62.5)	12 (75.0)
HEIGHT (CM)	N	8	8	16
	MEAN	144.1	145.5	144.8
	SD	17.13	14.46	15.33
	MEDIAN	145.9	144.6	144.6
	MIN	117	127	117
	MAX	166	166	166
BMI	N	8	8	16
	MEAN	26.53	23.36	24.94
	SD	8.505	6.306	7.415
	MEDIAN	24.50	23.15	24.05
	MIN	18.7	15.4	15.4
	MAX	45.2	32.8	45.2
BMI PERCENTILE	N	8	8	16
	MEAN	92.53	79.72	86.12
	SD	8.363	27.036	20.434
	MEDIAN	94.69	95.28	94.80
	MIN	74.7	24.1	24.1
	MAX	99.7	99.2	99.7

Baseline disease characteristics for the entire study population and the paediatric subgroup are summarised in Tables 4 and 5.

Table 4. Summary of Baseline Disease Characteristics, All Randomised and Treated Subjects

	ABATACEPT N = 17	PLACEBO N = 19	TOTAL N = 36
APOL1			
HIGH RISK	0	1(5.3)	1(2.8)
OTHERS	17(100.0)	18(94.7)	35(97.2)
SERUM ALBUMIN AT BASELINE (G/DL)			
N	17	19	36
MEAN (SD)	2.19(0.534)	2.62(0.634)	2.42(0.620)
MEDIAN (RANGE)	2.30(1.3 , 3.1)	2.60(1.5 , 3.8)	2.50(1.3 , 3.8)
UPCR AT BASELINE (MG/MG)			
N	17	19	36
MEAN (SD)	8.74(5.653)	7.18(3.465)	7.92(4.627)
MEDIAN (RANGE)	7.25(1.2 , 21.6)	5.84(3.0 , 15.6)	6.98(1.2 , 21.6)
eGFR AT BASELINE (ML/MIN / 1.73 M2)			
N	17	19	36
MEAN (SD)	84.27(35.426)	90.05(36.076)	87.32(35.378)
MEDIAN (RANGE)	84.03(32.8 ,157.6)	95.21(38.8 ,163.7)	92.10(32.8 ,163.7)
DURATION OF MCD (MONTHS)			
N	5	11	16
MEAN (SD)	37.85(36.610)	46.79(46.302)	44.00(42.485)
MEDIAN (RANGE)	29.80(6.6 , 98.0)	22.70(6.2 ,130.5)	26.25(6.2 ,130.5)
DURATION OF FSGS (MONTHS)			
N	12	8	20
MEAN (SD)	60.60(47.131)	55.58(31.605)	58.60(40.748)
MEDIAN (RANGE)	43.07(9.1 ,138.1)	48.03(11.9 ,106.4)	43.07(9.1 ,138.1)
RANDOMIZATION STRATA			
APOL1 (HIGH RISK) AND AGE (<18 YEARS)	0	0	0
APOL1 (HIGH RISK) AND AGE (>=18 YEARS)	0	1(5.3)	1(2.8)
APOL1 (OTHERS) AND AGE (<18 YEARS)	8(47.1)	8(42.1)	16(44.4)
APOL1 (OTHERS) AND AGE (>=18 YEARS)	9(52.9)	10(52.6)	19(52.8)

Baseline is Day 1 of the study.
UPCR = Protein/creatinine ratio (mg/mg) at baseline; eGFR = estimated Glomerular Filtration Rate (mL/min per 1.73m2) at baseline.

Table 5. Summary of Baseline Disease Characteristics, All Randomised and Treated Paediatric Subjects

	ABATACEPT N = 8	PLACEBO N = 8	TOTAL N = 16
APOL1			
HIGH RISK	0	0	0
OTHERS	8(100.0)	8(100.0)	16(100.0)
SERUM ALBUMIN AT BASELINE (G/DL)			
N	8	8	16
MEAN (SD)	2.05(0.558)	2.41(0.749)	2.23(0.665)
MEDIAN (RANGE)	2.10(1.3 , 2.7)	2.50(1.5 , 3.8)	2.45(1.3 , 3.8)
UPCR AT BASELINE (MG/MG)			
N	8	8	16
MEAN (SD)	8.33(6.524)	9.72(3.419)	9.02(5.083)
MEDIAN (RANGE)	6.33(1.2 , 21.6)	10.63(4.9 , 15.6)	9.26(1.2 , 21.6)
eGFR AT BASELINE (ML/MIN / 1.73 M2)			
N	8	8	16
MEAN (SD)	99.12(38.900)	95.66(46.225)	97.39(41.309)
MEDIAN (RANGE)	100.63(39.6 ,157.6)	90.96(38.8 ,163.7)	96.99(38.8 ,163.7)
DURATION OF MCD (MONTHS)			
N	4	6	10
MEAN (SD)	36.57(42.142)	31.84(32.849)	33.73(34.604)
MEDIAN (RANGE)	20.83(6.6 , 98.0)	16.85(6.2 , 90.5)	17.03(6.2 , 98.0)
DURATION OF FSGS (MONTHS)			
N	4	2	6
MEAN (SD)	71.63(48.881)	75.05(24.065)	72.77(39.402)
MEDIAN (RANGE)	59.75(28.9 ,138.1)	75.05(58.0 , 92.1)	67.87(28.9 ,138.1)

Baseline is Day 1 of the study.
UPCR = Protein/creatinine ratio (mg/mg) at baseline; eGFR = estimated Glomerular Filtration Rate (mL/min per 1.73m2) at baseline.

Efficacy results

Subject disposition

Subject disposition is summarised in Table 6. A total of 27 subjects (75%) completed the double-blind period, and 22 (61.1%) were treated in Period 2 (with the remaining 5 subjects entering OLE directly after the double-blind period as per amended study design). A total of 23 subjects (63.9%) were treated in OLE, and 10 subjects (27.8%) completed OLE. In all periods, lack of efficacy was the most common reason for discontinuation, while very few subjects discontinued due to an adverse event.

Table 6. Subject Disposition

	Number (%) of Subjects		
	ABATACEPT N = 17	PLACEBO N = 19	Total N = 36
NUMBER DISCONTINUED DOUBLE-BLIND PERIOD	3 (17.6)	6 (31.6)	9 (25.0)
DEATH	0	0	0
ADVERSE EVENT	1 (5.9)	2 (10.5)	3 (8.3)
LACK OF EFFICACY	1 (5.9)	3 (15.8)	4 (11.1)
LOST TO FOLLOW-UP	0	0	0
WITHDRAWAL OF CONSENT	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	1 (5.3)	1 (2.8)
SUBJ REQUEST TO DISCONTINUE STUDY TRT	0	0	0
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	1 (5.9)	0	1 (2.8)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
OTHER	0	0	0
NUMBER DISCONTINUED PERIOD 2	5 (29.4)	2 (10.5)	7 (19.4)
DEATH	0	0	0
ADVERSE EVENT	1 (5.9)	0	1 (2.8)
LACK OF EFFICACY	1 (5.9)	2 (10.5)	3 (8.3)
LOST TO FOLLOW-UP	0	0	0
WITHDRAWAL OF CONSENT	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (5.9)	0	1 (2.8)
SUBJ REQUEST TO DISCONTINUE STUDY TRT	1 (5.9)	0	1 (2.8)
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
OTHER	1 (5.9)	0	1 (2.8)
NUMBER DISCONTINUED OPEN-LABEL PERIOD	4 (23.5)	9 (47.4)	13 (36.1)
DEATH	0	0	0
ADVERSE EVENT	0	1 (5.3)	1 (2.8)
LACK OF EFFICACY	3 (17.6)	5 (26.3)	8 (22.2)
LOST TO FOLLOW-UP	0	1 (5.3)	1 (2.8)
WITHDRAWAL OF CONSENT	0	0	0
SUBJECT NO LONGER MEETS STUDY CRITERIA	0	0	0
SUBJ REQUEST TO DISCONTINUE STUDY TRT	1 (5.9)	0	1 (2.8)
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	0	0	0
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
OTHER	0	2 (10.5)	2 (5.6)
NUMBER COMPLETED DOUBLE-BLIND PERIOD	14 (82.4)	13 (68.4)	27 (75.0)
NUMBER COMPLETED DOUBLE-BLIND PERIOD AND ENTERED OLE	3 (17.6)	2 (10.5)	5 (13.9)
NUMBER OF PEDIATRIC SUBJECTS WHO EARLY ESCAPED TO OLE AT DAY 85	1 (5.9)	2 (10.5)	3 (8.3)
NUMBER COMPLETED DOUBLE-BLIND PERIOD BUT DID NOT ENTER OLE	0	0	0
NUMBER TREATED IN PERIOD 2	11 (64.7)	11 (57.9)	22 (61.1)
NUMBER COMPLETED PERIOD 2	6 (35.3)	9 (47.4)	15 (41.7)
NUMBER COMPLETED PERIOD 2 AND ENTERED OLE	5 (29.4)	9 (47.4)	14 (38.9)
NUMBER OF SUBJECTS WHO EARLY ESCAPED TO OLE IN PERIOD 2 DUE TO RENAL RELAPSE	1 (5.9)	0	1 (2.8)
NUMBER COMPLETED PERIOD 2 BUT DID NOT ENTER OLE	1 (5.9)	0	1 (2.8)
NUMBER TREATED IN OLE	10 (58.8)	13 (68.4)	23 (63.9)
NUMBER COMPLETED OLE	6 (35.3)	4 (21.1)	10 (27.8)

Period 2 rows are only for subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2.

Efficacy results

By Day 113 of the double-blind period, only one subject in the placebo group had reached the primary endpoint of Renal Response (Table 7). A breakdown of Renal Response by age group is displayed in Table 8.

Table 7. Summary of Renal Response and Complete Remission Over Time: All Randomised and Treated Subjects

Study Day			ABATACEPT N = 17	PLACEBO N = 19
DOUBLE-BLIND DAY 113	RENAL RESPONSE	NUMBER OF SUBJECTS, n/m (%)	0/13 (0.0%)	1/13 (7.7%)
		95% CI	(0.0 , 24.7)	(0.2 , 36.0)
		ESTIMATE OF DIFFERENCE (95% CI)	-7.7 (-46.8 , 33.3)	N/A
	COMPLETE REMISSION	NUMBER OF SUBJECTS, n/m (%)	0/13 (0.0%)	0/13 (0.0%)
		95% CI	(0.0 , 24.7)	(0.0 , 24.7)
		ESTIMATE OF DIFFERENCE (95% CI)	N/A	N/A
OPEN LABEL DAY 113	RENAL RESPONSE	NUMBER OF SUBJECTS, n/m (%)	1/8 (12.5%)	3/9 (33.3%)
		95% CI	(0.3 , 52.7)	(7.5 , 70.1)
		ESTIMATE OF DIFFERENCE (95% CI)	-20.8 (-63.3 , 24.3)	N/A
	COMPLETE REMISSION	NUMBER OF SUBJECTS, n/m (%)	1/8 (12.5%)	1/9 (11.1%)
		95% CI	(0.3 , 52.7)	(0.3 , 48.2)
		ESTIMATE OF DIFFERENCE (95% CI)	1.4 (-44.7 , 44.7)	N/A

n = Number of subjects with response, m = Number of subjects in the analysis.
Renal Response is defined as a meeting all the following criteria:
PROTEINURIA: Reduction of baseline urine protein/creatinine ratio (UPCR) of >= 50% and to less than 3.
RENAL FUNCTION: No worsening of baseline estimated glomerular filtration rate (eGFR) defined as within normal range if normal at baseline or >= 75% baseline value if below normal at baseline.
Complete Remission is defined as a meeting all the following criteria:
PROTEINURIA: urine protein/creatinine ratio (UPCR) less or equal to 3.
RENAL FUNCTION: No worsening of baseline estimated glomerular filtration rate (eGFR) defined as within normal range if normal at baseline or >= 75% baseline value if below normal at baseline.
Treatment differences and 95% CI based on minimum risk weights when n greater than or equal to 5, otherwise exact method is used.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2 and OLE data.

Table 8. Proportion of Subjects in Renal Response Over Time by Age Group: All Randomised and Treated Subjects

Study Day	Subgroup		ABATACEPT N = 17	PLACEBO N = 19	TOTAL N = 36
DOUBLE-BLIND DAY 113	6-11	NUMBER OF SUBJECTS, n/m (%)	0/2 (0.0%)	1/4 (25.0%)	1/6 (16.7%)
		95% CI	(0.0 , 84.2)	(0.6 , 80.6)	(0.4 , 64.1)
		ESTIMATE OF DIFFERENCE (95% CI)	-25.0(-67.4 , 17.4)	N/A	N/A
	12-<18	NUMBER OF SUBJECTS, n/m (%)	0/3 (0.0%)	0/1 (0.0%)	0/4 (0.0%)
		95% CI	(0.0 , 70.8)	(0.0 , 97.5)	(0.0 , 60.2)
		ESTIMATE OF DIFFERENCE (95% CI)	NE	N/A	N/A
	>=18	NUMBER OF SUBJECTS, n/m (%)	0/8 (0.0%)	0/8 (0.0%)	0/16 (0.0%)
		95% CI	(0.0 , 36.9)	(0.0 , 36.9)	(0.0 , 20.6)
		ESTIMATE OF DIFFERENCE (95% CI)	NE	N/A	N/A
OPEN LABEL DAY 113	6-11	NUMBER OF SUBJECTS, n/m (%)	1/3 (33.3%)	1/2 (50.0%)	2/5 (40.0%)
		95% CI	(0.8 , 90.6)	(1.3 , 98.7)	(5.3 , 85.3)
		ESTIMATE OF DIFFERENCE (95% CI)	-16.7(-100 , 70.8)	N/A	N/A
	12-<18	NUMBER OF SUBJECTS, n/m (%)	0/2 (0.0%)	0/1 (0.0%)	0/3 (0.0%)
		95% CI	(0.0 , 84.2)	(0.0 , 97.5)	(0.0 , 70.8)
		ESTIMATE OF DIFFERENCE (95% CI)	NE	N/A	N/A
	>=18	NUMBER OF SUBJECTS, n/m (%)	0/3 (0.0%)	2/6 (33.3%)	2/9 (22.2%)
		95% CI	(0.0 , 70.8)	(4.3 , 77.7)	(2.8 , 60.0)
		ESTIMATE OF DIFFERENCE (95% CI)	-33.3(-71.1 , 4.4)	N/A	N/A

n = Number of subjects with response, m = Number of subjects in the analysis.
Renal Response is defined as a meeting all the following criteria:
PROTEINURIA: Reduction of baseline urine protein/creatinine ratio (UPCR) of >= 50% and to less than 3.
RENAL FUNCTION: No worsening of baseline estimated glomerular filtration rate (eGFR) defined as within normal range if normal at baseline or >= 75% baseline value if below normal at baseline.
Treatment differences and 95% CI are based on normal approximation. (without any adjustments for strata) when n greater than or equal to 5, otherwise exact method is used.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2 and OLE data.

Changes from baseline in UPCR, serum albumin or eGFR were very small, and there were no differences between treatment groups (Table 9). Very little effect was seen on any domain of the PROMIS measures.

Table 9. Mean Change from Baseline in UPCR, Serum Albumin and eGFR at Day 113: All Randomised and Treated Subjects

	Study Day		ABATACEPT N = 17	PLACEBO N = 19
UPCR (mg/mg)	DOUBLE-BLIND DAY 113	n	13	13
		BASELINE MEAN (SD)	8.66 (6.349)	7.07 (3.877)
		POST-BASELINE MEAN (SD)	8.78 (6.598)	6.82 (3.181)
		MEAN CHANGE FROM BASELINE (SE)	0.12 (0.5738)	-0.25 (0.7914)
		95% CI	(-1.13 , 1.37)	(-1.97 , 1.48)
		MEAN DIFFERENCE FROM PLACEBO (95% CI)	0.37 (-1.6495 , 2.3855)	
Serum Albumin (g/dL)	DOUBLE-BLIND DAY 113	n	11	12
		BASELINE MEAN (SD)	2.35 (0.501)	2.75 (0.605)
		POST-BASELINE MEAN (SD)	2.43 (0.400)	2.70 (0.621)
		MEAN CHANGE FROM BASELINE (SE)	0.08 (0.1016)	-0.05 (0.0892)
		95% CI	(-0.14 , 0.31)	(-0.25 , 0.15)
		MEAN DIFFERENCE FROM PLACEBO (95% CI)	0.13 (-0.1483 , 0.4119)	
Glomerular Filtration Rate (eGFR)	DOUBLE-BLIND DAY 113	n	11	12
		BASELINE MEAN (SD)	75.37 (29.895)	91.86 (32.704)
		POST-BASELINE MEAN (SD)	73.32 (37.485)	90.44 (28.825)
		MEAN CHANGE FROM BASELINE (SE)	-2.05 (2.8005)	-1.43 (2.4504)
		95% CI	(-8.29 , 4.19)	(-6.82 , 3.97)
		MEAN DIFFERENCE FROM PLACEBO (95% CI)	-0.62 (-8.3287 , 7.0855)	

n is the number of subjects with both post-baseline and baseline measurements.
Estimated Glomerular Filtration Rate was calculated using the CKD-EPI formula for adults and Schwartz formula for pediatrics.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2 and OLE data.

Safety results

Extent of exposure

During the double-blind period, 27 subjects (75%) received 5 infusions of medication and 9 subjects (25%) received 3-4 infusions. The mean (SD) number of days of exposure was 105.4 (15.75) days (Table 10).

Table 10. Extent of Exposure (Number of Days) to Study Medication During the Double-Blind Period: All Randomised and Treated Subjects

	Number (%) of Subjects		
Days of Exposure	ABATACEPT N = 17	PLACEBO N = 19	TOTAL N = 36
<=57	0	0	0
58-85	2 (11.8)	3 (15.8)	5 (13.9)
86-120	14 (82.4)	16 (84.2)	30 (83.3)
>120	1 (5.9)	0	1 (2.8)
MEAN (SD)	106.5 (19.27)	104.4 (12.25)	105.4 (15.75)
MEDIAN (RANGE)	112.0 (58, 148)	112.0 (79, 115)	112.0 (58, 148)

Interruptions in therapy were not deducted from calculation of days of exposure.
For subjects who discontinued the study before entering the next Period: Days of Exposure = [(date of the last dose in the Period - date of the first dose in the Period + 1) + 56)].
For subjects continuing to the next Period: Days of Exposure = ([date of the first dose in the next Period - date of the first dose in the Period] - adjustment). Adjustment is the period after 56 days from last dose in the Period to the first dose in the next Period.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to the first dose in Period 2.

Overall, 32 of the 36 enrolled subjects were exposed to abatacept during the entire study.

Adverse events

A summary of AEs during the double-blind period by age group is displayed in Table 11, and a corresponding summary for the cumulative abatacept period in Table 12.

Table 11. Adverse Event Summary During Double-Blind Period and by Age Group- All Treated Subjects

All Treated Subjects

	Number (%) of Subjects		
	Abatacept (N = 17)	Placebo (N = 19)	TOTAL (N = 36)
DEATHS	0	0	0
SAES	5 (29.4)	4 (21.1)	9 (25.0)
RELATED SAES	0	1 (5.3)	1 (2.8)
DISCONTINUED DUE TO SAES	1 (5.9)	1 (5.3)	2 (5.6)
AES	13 (76.5)	15 (78.9)	28 (77.8)
RELATED AES	6 (35.3)	4 (21.1)	10 (27.8)
DISCONTINUED DUE TO AES	1 (5.9)	2 (10.5)	3 (8.3)

Subgroup : 6-11 years

	Number (%) of Subjects		
	Abatacept (N = 4)	Placebo (N = 5)	TOTAL (N = 9)
DEATHS	0	0	0
SAES	2 (50.0)	1 (20.0)	3 (33.3)
RELATED SAES	0	1 (20.0)	1 (11.1)
DISCONTINUED DUE TO SAES	1 (25.0)	0	1 (11.1)
AES	4 (100.0)	3 (60.0)	7 (77.8)
RELATED AES	0	1 (20.0)	1 (11.1)
DISCONTINUED DUE TO AES	1 (25.0)	0	1 (11.1)

Subgroup : 12-<18 years

	Number (%) of Subjects		
	Abatacept (N = 4)	Placebo (N = 3)	TOTAL (N = 7)
DEATHS	0	0	0
SAES	2 (50.0)	2 (66.7)	4 (57.1)
RELATED SAES	0	0	0
DISCONTINUED DUE TO SAES	0	1 (33.3)	1 (14.3)
AES	4 (100.0)	3 (100.0)	7 (100.0)
RELATED AES	3 (75.0)	0	3 (42.9)
DISCONTINUED DUE TO AES	0	1 (33.3)	1 (14.3)

Subgroup: >=18 years

	Number (%) of Subjects		
	Abatacept (N = 9)	Placebo (N = 11)	TOTAL (N = 20)
DEATHS	0	0	0
SAES	1 (11.1)	1 (9.1)	2 (10.0)
RELATED SAES	0	0	0
DISCONTINUED DUE TO SAES	0	0	0
AES	5 (55.6)	9 (81.8)	14 (70.0)
RELATED AES	3 (33.3)	3 (27.3)	6 (30.0)
DISCONTINUED DUE TO AES	0	1 (9.1)	1 (5.0)

Includes data up to 56 days post last dose date in Double-Blind Period or up to first dose date/time in Open-Label Period whichever is earlier.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2.
All deaths that occurred in subjects treated in the Period but did not enter the next Period are included in this summary regardless of when they occur.
SAEs include hospitalizations for elective surgical procedures.
Related AE or SAE defined as AE or SAE with Related or Missing relationship to study medication.
MEDDRA VERSION: 22.1

Table 12. Adverse Event Summary the Cumulative Abatacept Period and by Age Group- All Treated Abatacept Subjects

	Number (%) of Subjects Abatacept (N=32)
Deaths	0
SAEs	10 (31.3)
Related SAEs	0
Discontinued due to SAEs	1 (3.1)
AEs	26 (81.3)
Related AEs	10 (31.3)
Discontinued due to AEs	2 (6.3)

Subgroup : 6-11 years

	Number (%) of Subjects Abatacept (N = 9)
DEATHS	0
SAES	4 (44.4)
RELATED SAES	0
DISCONTINUED DUE TO SAES	1 (11.1)
AES	7 (77.8)
RELATED AES	1 (11.1)
DISCONTINUED DUE TO AES	2 (22.2)

Subgroup : 12-<18 years

	Number (%) of Subjects Abatacept (N = 6)
DEATHS	0
SAES	4 (66.7)
RELATED SAES	0
DISCONTINUED DUE TO SAES	0
AES	6 (100.0)
RELATED AES	4 (66.7)
DISCONTINUED DUE TO AES	0

Subgroup : >=18 years

	Number (%) of Subjects Abatacept (N = 17)
DEATHS	0
SAES	2 (11.8)
RELATED SAES	0
DISCONTINUED DUE TO SAES	0
AES	13 (76.5)
RELATED AES	5 (29.4)
DISCONTINUED DUE TO AES	0

Includes data up to 56 days post last Abatacept dose date.
SAEs include hospitalizations for elective surgical procedures.
Related AE or SAE defined as AE or SAE with Related or Missing relationship to study medication.
MEDDRA VERSION: 22.1

No deaths were reported during the study. SAEs were reported in 9 subjects during the double-blind period (5 in the abatacept group and 4 in the placebo group; Table 13). Of these, one SAE was considered related to study drug; this was a case of Grade 1 lip swelling on study day 6 in a subject assigned to placebo. The event resolved on day 8 and no action was taken concerning the study drug. During the cumulative abatacept period, a total of 10 subjects experienced an SAE (Table 14).

Table 13. Serious Adverse Events Reported During Double-Blind Period: All Treated Subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept (N = 17)	Placebo (N = 19)	TOTAL (N = 36)
TOTAL SUBJECTS WITH AE	5 (29.4)	4 (21.1)	9 (25.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (23.5)	1 (5.3)	5 (13.9)
GENERALISED OEDEMA	2 (11.8)	0	2 (5.6)
OEDEMA	2 (11.8)	0	2 (5.6)
CHEST PAIN	1 (5.9)	0	1 (2.8)
OEDEMA PERIPHERAL	0	1 (5.3)	1 (2.8)
RENAL AND URINARY DISORDERS	1 (5.9)	3 (15.8)	4 (11.1)
ACUTE KIDNEY INJURY	0	2 (10.5)	2 (5.6)
NEPHROTIC SYNDROME	1 (5.9)	1 (5.3)	2 (5.6)
RENAL TUBULAR NECROSIS	0	1 (5.3)	1 (2.8)
GASTROINTESTINAL DISORDERS	0	2 (10.5)	2 (5.6)
DIARRHOEA	0	1 (5.3)	1 (2.8)
LIP SWELLING	0	1 (5.3)	1 (2.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (5.9)	0	1 (2.8)
ANAEMIA	1 (5.9)	0	1 (2.8)
EYE DISORDERS	0	1 (5.3)	1 (2.8)
PERIORBITAL SWELLING	0	1 (5.3)	1 (2.8)
METABOLISM AND NUTRITION DISORDERS	1 (5.9)	0	1 (2.8)
FLUID OVERLOAD	1 (5.9)	0	1 (2.8)
METABOLIC ACIDOSIS	1 (5.9)	0	1 (2.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (5.3)	1 (2.8)
ASTHMA	0	1 (5.3)	1 (2.8)

Includes data up to 56 days post last dose date in Double-Blind Period or up to first dose date/time in Open-Label Period whichever is earlier.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2.
MEDDRA VERSION: 22.1

Table 14. Serious Adverse Events Reported During the Cumulative Abatacept Period: All Treated Abatacept Subjects

SYSTEM ORGAN CLASS (SOC) (%) PREFERRED TERM (PT) (%)	Abatacept (N = 32)
TOTAL SUBJECTS WITH AE	10 (31.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (12.5)
GENERALISED OEDEMA	3 (9.4)
OEDEMA	2 (6.3)
CHEST PAIN	1 (3.1)
RENAL AND URINARY DISORDERS	4 (12.5)
ACUTE KIDNEY INJURY	1 (3.1)
NEPHROTIC SYNDROME	1 (3.1)
RENAL DISORDER	1 (3.1)
RENAL FAILURE	1 (3.1)
RENAL IMPAIRMENT	1 (3.1)
INVESTIGATIONS	2 (6.3)
BLOOD CREATININE INCREASED	2 (6.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (3.1)
ANAEMIA	1 (3.1)
CARDIAC DISORDERS	1 (3.1)
PALPITATIONS	1 (3.1)
INFECTIONS AND INFESTATIONS	1 (3.1)
PARAINFLUENZAE VIRUS INFECTION	1 (3.1)
PNEUMONIA	1 (3.1)
METABOLISM AND NUTRITION DISORDERS	1 (3.1)
FLUID OVERLOAD	1 (3.1)
METABOLIC ACIDOSIS	1 (3.1)
NERVOUS SYSTEM DISORDERS	1 (3.1)
SEIZURE	1 (3.1)

Includes data up to 56 days post last Abatacept dose date.
MEDDRA VERSION: 22.1

The MAH has separately highlighted four SAEs as follows: one subject had new onset of reported seizures 7 weeks after the last infusion of abatacept; one subject had a complex medical event characterised by acute kidney injury associated with thrombotic microangiopathy and pneumonia due to RSV, almost 4 months after the last dose of abatacept; one subject developed a tunnel graft

infection over 6 months after last abatacept dose; and one subject develop a parainfluenza virus pneumonia after their 3rd dose of abatacept (this was the only serious infection associated with abatacept use).

During the double-blind period, three subjects (8.3%) experienced an AE that led to discontinuation: in the abatacept group, 1 subject discontinued due to fluid overload, and in the placebo group, 1 subject discontinued due to influenza and another subject due to acute kidney injury. During the cumulative abatacept period, 2 subjects (6.3%) had an AE that led to discontinuation (1 subject with diarrhoea, face oedema and non-cardiac chest pain, and 1 subject with fluid overload).

Most frequently reported AEs across both dose groups during the double-blind period are displayed in Table 15. During the cumulative abatacept period, the most frequently reported AEs were nausea (25%), diarrhoea (21.9%), vomiting (21.9%), headache (18.8%) and upper respiratory tract infection (15.6%).

Table 15. Most Frequently Reported Adverse Events during the Double-Blind Period: All Treated Subjects

Preferred Term (PT) (%)	Abatacept N = 17	Placebo N = 19	Total N = 36
TOTAL SUBJECTS WITH AE	13 (76.5)	15 (78.9)	28 (77.8)
DIARRHOEA	4 (23.5)	4 (21.1)	8 (22.2)
HEADACHE	2 (11.8)	5 (26.3)	7 (19.4)
VOMITING	5 (29.4)	2 (10.5)	7 (19.4)
OEDEMA	4 (23.5)	2 (10.5)	6 (16.7)
NAUSEA	2 (11.8)	2 (10.5)	4 (11.1)
COUGH	1 (5.9)	2 (10.5)	3 (8.3)
DIZZINESS	3 (17.6)	0	3 (8.3)
OEDEMA PERIPHERAL	0	3 (15.8)	3 (8.3)
PYREXIA	1 (5.9)	2 (10.5)	3 (8.3)
ACUTE KIDNEY INJURY	0	2 (10.5)	2 (5.6)
ARTHRALGIA	0	2 (10.5)	2 (5.6)
ASTHMA	1 (5.9)	1 (5.3)	2 (5.6)
BLOOD CREATININE INCREASED	0	2 (10.5)	2 (5.6)
CHEST PAIN	2 (11.8)	0	2 (5.6)
DECREASED APPETITE	1 (5.9)	1 (5.3)	2 (5.6)
GASTROENTERITIS VIRAL	2 (11.8)	0	2 (5.6)
GENERALISED OEDEMA	2 (11.8)	0	2 (5.6)
GOUT	1 (5.9)	1 (5.3)	2 (5.6)
HYPERTENSION	0	2 (10.5)	2 (5.6)
HYPOTHYROIDISM	2 (11.8)	0	2 (5.6)
INFUSION RELATED REACTION	2 (11.8)	0	2 (5.6)
NEPHROTIC SYNDROME	1 (5.9)	1 (5.3)	2 (5.6)
OROPHARYNGEAL PAIN	0	2 (10.5)	2 (5.6)
TACHYCARDIA	1 (5.9)	1 (5.3)	2 (5.6)
ABDOMINAL DISCOMFORT	0	1 (5.3)	1 (2.8)
ABDOMINAL PAIN	1 (5.9)	0	1 (2.8)
ABDOMINAL PAIN UPPER	1 (5.9)	0	1 (2.8)

Includes data up to 56 days post last dose date in Double-Blind Period or up to first dose date/time in Open-Label Period whichever is earlier.
For subjects who completed Period 1 and entered Period 2 prior to Protocol Amendment 2, includes data from first dose date in Period 1 up to first dose in Period 2.
MEDDRA VERSION: 22.1

Among pre-specified AEs of special interest, peri-infusional AEs were more frequent with abatacept than placebo. Other AEs of special interest were equally distributed between treatment groups, the most common AE of special interest being an infection in both groups (Table 16).

Table 16. Adverse Events of Special Interest: All Treated Subjects

	Abatacept N = 17	Placebo N=19
Peri-infusional AE, n	6	3
AE within 24 hours of Infusion, n	8	9
Malignancies, n	0	0
Infections/Infestations, n	12	10
Autoimmune disorders (pre-specified), n	0	1

There were no particular findings in clinical laboratory assessments. The most frequent laboratory abnormality was a low total protein concentration, observed in 4 subjects on abatacept and 6 subjects on placebo.

According to the MAH, the overall safety observed was consistent with that seen in abatacept trials and more favourable than that seen in randomised controlled trials with abatacept for the treatment of active lupus nephritis.

Pharmacokinetic and immunogenicity results

In study IM101566, PK blood samples were obtained pre-dose and 0.5 hours post-dose in relation to each study drug administration. In addition, samples were collected at 1 week intervals between study days 85 and 113 for determination of the area under the serum time curve over a dosing interval (AUCtau). Trough (Cmin) and maximum observed serum concentrations (Cmax) and AUCtau are summarised in Table 17. The results in the overall populations showed that trough concentration did not reach therapeutic levels of 10 ug/mL, with the exception of Day 29 within the adult population. According to the MAH, the detrimental effects of ongoing proteinuria contributed to the observed PK, and the lower exposures compared to those seen in non-proteinuric patients were therefore as expected.

Table 17. Summary Statistics of Abatacept Cmin (ug/mL) Values Over Time and AUCtau (ug*h/mL) Values Between Days 85 and 113 by Age Group: PK Analysis Population

CMIN (ug/mL)

		Adults (>= 18 Years)					Pediatric (6-17 Years)				
Treatment	Statistic	DAY 15	DAY 29	DAY 57	DAY 85	DAY 113	DAY 15	DAY 29	DAY 57	DAY 85	DAY 113
Abatacept	N	9	8	9	7	7	8	7	8	5	6
	MEAN	10.153	15.619	4.709	4.676	3.703	5.562	6.775	2.463	5.540	4.022
	S.D.	6.470	13.546	3.130	2.464	2.524	6.472	9.399	3.526	6.844	6.559
	GEO.MEAN	7.613	12.274	3.641	4.101	2.786	2.829	2.588	0.504	1.617	0.990
	% CV	63.7	86.7	66.5	52.7	68.2	116.4	138.7	143.2	123.5	163.1
	MEDIAN	11.700	12.065	3.990	4.100	3.440	2.715	2.940	0.944	2.140	1.745
	MIN	1.20	5.02	0.50	2.05	0.49	0.15	0.09	0.00	0.03	0.02
	MAX	19.90	47.20	11.20	7.95	7.80	20.10	26.90	10.30	16.80	17.20

Cmin values reported as <LLOQ are imputed as LLOQ/2 (LLOQ is 0.001 ug/mL).

AUCTAU (h*ug/mL)

		Adults (>= 18 Years)	Pediatric (6-17 Years)
Treatment	Statistic	DAY 85	DAY 85
Abatacept	N	7	4
	MEAN	22173.633	19702.841
	S.D.	9813.756	8259.538
	GEO.MEAN	20394.832	18282.500
	% CV	44.3	41.9
	MEDIAN	20986.134	19757.115
	MIN	10635.59	10040.02
	MAX	37704.84	29257.11

In study IM101566, immunogenicity was evaluated at Day 1 (Baseline) and at Day 113. For subjects who discontinued during or at the end of the Double-blind Treatment Period, immunogenicity was also evaluated 56, 84 and 168 days after the last dose of study medication. Immunogenicity results are summarised in Table 18. In the abatacept group, 1 out of 14 subjects (7.1%) had a positive CTLA4 and possibly Ig response at Day 113, and 3 out of 7 subjects (42.9%) had a positive CTLA4 and possibly Ig response during post-treatment visits. In the placebo group, no subjects had a positive response at Day 113, whereas 2 out of 5 subjects (40.0%) had a positive CTLA4 and possibly Ig response during post-treatment visits. No paediatric subjects in the abatacept group had a positive response either during or post treatment, whereas in the placebo group, one paediatric subject developed a positive response post treatment. According to the MAH, the presence of anti-drug antibodies had no effect on the PK or safety.

Table 18. Proportion of Subjects with Positive Antibody Response to Abatacept Relative to Baseline (ECL Method) Over Time: Immunogenicity Analysis Population

Treatment Group	Age Group	Study Day	CTLA4 AND POSSIBLY IG n/m (%)	IG AND/OR JUNCTION REGION n/m (%)	Total n/m (%)
ABATACEPT	ADULT	DAY 113	1 / 8 (12.5%)	0 / 8	1 / 8 (12.5%)
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	1 / 8 (12.5%)	0 / 8	1 / 8 (12.5%)
		56 DAYS POST LAST DOSE	2 / 3 (66.7%)	0 / 3	2 / 3 (66.7%)
		84 DAYS POST LAST DOSE	2 / 4 (50.0%)	0 / 4	2 / 4 (50.0%)
		168 DAYS POST LAST DOSE	1 / 3 (33.3%)	0 / 3	1 / 3 (33.3%)
		OVERALL POST VISITS	3 / 4 (75.0%)	0 / 4	3 / 4 (75.0%)
		OVERALL	4 / 8 (50.0%)	0 / 8	4 / 8 (50.0%)
	PEDIATRIC	DAY 113	0 / 6	0 / 6	0 / 6
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	0 / 6	0 / 6	0 / 6
		56 DAYS POST LAST DOSE	0 / 2	0 / 2	0 / 2
		84 DAYS POST LAST DOSE	0 / 3	0 / 3	0 / 3
		168 DAYS POST LAST DOSE	0 / 3	0 / 3	0 / 3
		OVERALL POST VISITS	0 / 3	0 / 3	0 / 3
		OVERALL	0 / 6	0 / 6	0 / 6
	TOTAL	DAY 113	1 / 14 (7.1%)	0 / 14	1 / 14 (7.1%)
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	1 / 14 (7.1%)	0 / 14	1 / 14 (7.1%)
		56 DAYS POST LAST DOSE	2 / 5 (40.0%)	0 / 5	2 / 5 (40.0%)
		84 DAYS POST LAST DOSE	2 / 7 (28.6%)	0 / 7	2 / 7 (28.6%)
		168 DAYS POST LAST DOSE	1 / 6 (16.7%)	0 / 6	1 / 6 (16.7%)
		OVERALL POST VISITS	3 / 7 (42.9%)	0 / 7	3 / 7 (42.9%)
		OVERALL	4 / 14 (28.6%)	0 / 14	4 / 14 (28.6%)
PLACEBO	ADULT	DAY 113	0 / 7	0 / 7	0 / 7
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	0 / 7	0 / 7	0 / 7
		56 DAYS POST LAST DOSE	1 / 1 (100.0%)	0 / 1	1 / 1 (100.0%)
		84 DAYS POST LAST DOSE	1 / 1 (100.0%)	0 / 1	1 / 1 (100.0%)
		168 DAYS POST LAST DOSE	0 / 2	0 / 2	0 / 2
		OVERALL POST VISITS	1 / 2 (50.0%)	0 / 2	1 / 2 (50.0%)
		OVERALL	1 / 7 (14.3%)	0 / 7	1 / 7 (14.3%)
	PEDIATRIC	DAY 113	0 / 5	0 / 5	0 / 5
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	0 / 5	0 / 5	0 / 5
		56 DAYS POST LAST DOSE	1 / 2 (50.0%)	0 / 2	1 / 2 (50.0%)
		84 DAYS POST LAST DOSE	1 / 2 (50.0%)	0 / 2	1 / 2 (50.0%)
		168 DAYS POST LAST DOSE	1 / 2 (50.0%)	0 / 2	1 / 2 (50.0%)
		OVERALL POST VISITS	1 / 3 (33.3%)	0 / 3	1 / 3 (33.3%)
		OVERALL	1 / 5 (20.0%)	0 / 5	1 / 5 (20.0%)
	TOTAL	DAY 113	0 / 12	0 / 12	0 / 12
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	0 / 12	0 / 12	0 / 12
		56 DAYS POST LAST DOSE	2 / 3 (66.7%)	0 / 3	2 / 3 (66.7%)
		84 DAYS POST LAST DOSE	2 / 3 (66.7%)	0 / 3	2 / 3 (66.7%)
		168 DAYS POST LAST DOSE	1 / 4 (25.0%)	0 / 4	1 / 4 (25.0%)
		OVERALL POST VISITS	2 / 5 (40.0%)	0 / 5	2 / 5 (40.0%)
		OVERALL	2 / 12 (16.7%)	0 / 12	2 / 12 (16.7%)
TOTAL	ADULT	DAY 113	1 / 15 (6.7%)	0 / 15	1 / 15 (6.7%)
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	1 / 15 (6.7%)	0 / 15	1 / 15 (6.7%)
		56 DAYS POST LAST DOSE	3 / 4 (75.0%)	0 / 4	3 / 4 (75.0%)
		84 DAYS POST LAST DOSE	3 / 5 (60.0%)	0 / 5	3 / 5 (60.0%)
		168 DAYS POST LAST DOSE	1 / 5 (20.0%)	0 / 5	1 / 5 (20.0%)
		OVERALL POST VISITS	4 / 6 (66.7%)	0 / 6	4 / 6 (66.7%)
		OVERALL	5 / 15 (33.3%)	0 / 15	5 / 15 (33.3%)
	PEDIATRIC	DAY 113	0 / 11	0 / 11	0 / 11
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	0 / 11	0 / 11	0 / 11
		56 DAYS POST LAST DOSE	1 / 4 (25.0%)	0 / 4	1 / 4 (25.0%)
		84 DAYS POST LAST DOSE	1 / 5 (20.0%)	0 / 5	1 / 5 (20.0%)
		168 DAYS POST LAST DOSE	1 / 5 (20.0%)	0 / 5	1 / 5 (20.0%)
		OVERALL POST VISITS	1 / 6 (16.7%)	0 / 6	1 / 6 (16.7%)
		OVERALL	1 / 11 (9.1%)	0 / 11	1 / 11 (9.1%)
	TOTAL	DAY 113	1 / 26 (3.8%)	0 / 26	1 / 26 (3.8%)
		OVERALL ON-TREATMENT DURING DOUBLE-BLIND PERIOD	1 / 26 (3.8%)	0 / 26	1 / 26 (3.8%)
		56 DAYS POST LAST DOSE	4 / 8 (50.0%)	0 / 8	4 / 8 (50.0%)
		84 DAYS POST LAST DOSE	4 / 10 (40.0%)	0 / 10	4 / 10 (40.0%)
		168 DAYS POST LAST DOSE	2 / 10 (20.0%)	0 / 10	2 / 10 (20.0%)
		OVERALL POST VISITS	5 / 12 (41.7%)	0 / 12	5 / 12 (41.7%)
		OVERALL	6 / 26 (23.1%)	0 / 26	6 / 26 (23.1%)

n = Number of subjects who are positive.
m = Number of subjects who are evaluated.
Immunogenicity is evaluated at Day 1 (Baseline), Day 113. For subjects who discontinue during or at the end of the Double-blind Treatment Period, immunogenicity is also evaluated 56, 84 and 168 days after the last dose of study medication. A positive response relative to baseline is defined as a positive response at a post-baseline visit that has a titer value greater than the positive baseline titer value. If the baseline titer is missing or negative, any post-baseline positive titer value is considered a positive response relative to baseline.

2.3.3. Discussion on clinical aspects

Study IM101566 was a double-blind placebo-controlled Phase 2 study to investigate the efficacy and safety of intravenous abatacept in the treatment of treatment resistant nephrotic syndrome. In principle, the design elements as described are considered adequate and fit for purpose. A mixed population of adult and paediatric subjects was to be enrolled, and randomisation was stratified by age. For purposes of Article 46, it should be noted that there was no specified minimum number of paediatric subjects.

Subject enrolment appears to have been challenging; moreover, a significant number of screened subjects failed to meet eligibility criteria. The study was terminated before the planned number of subjects had been randomised, and only 36 subjects, of which 16 subjects were in the paediatric age group, were ultimately treated with study drug in the double-blind period. Overall, 32 subjects, including 15 paediatric subjects, were exposed to abatacept during the entire study.

Overall, very few subjects demonstrated any signs of potential efficacy in respect of either the primary or secondary endpoints assessed. The overall safety profile was consistent with previous experience. The relatively low abatacept exposures observed in the study are readily explained by the underlying condition in the patient population studied.

In conclusion, this prematurely terminated Phase 2 study did not suggest that abatacept would have general applicability for treatment resistant nephrotic syndrome in either adult or paediatric subjects, and there was no significant new safety information. Considering the very limited sample size, no further conclusions can be made.

3. Rapporteur's overall conclusion and recommendation

The current study does not seem to support the use of abatacept in treatment resistant nephrotic syndrome (FSGS or MCD type), and no claims thereto are made by the MAH. In terms of paediatric use, no conclusions relevant to Article 46 can be made based on the few paediatric subjects treated within the study. Overall, the results of the study do not change the benefit-risk profile of abatacept in its currently approved indications for use. No changes to the current product information are warranted.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

None.