Sponsor
Novartis

Generic Drug Name
Tesidolumab

Trial Indication(s)
drug-drug interaction

Protocol Number
CLFG316B2101

Protocol Title
Open-label, parallel-group, drug-drug interaction study in end-stage renal disease patients awaiting kidney transplant to investigate the potential effect of IVIG treatment on the pharmacokinetics and pharmacodynamics of LFG316

Clinical Trial Phase
Phase I

Phase of Drug Development
Phase II

Study Start/End Dates
26 Aug 2016 to 19 Jul 2017

Reason for Termination (If applicable)

Due to strategic reasons, Novartis decided to halt development of LFG316 in AMR indication. It was informed to FDA in May 2017. Subsequently, it was decided to terminate the study after the eighth patient completed the study in July 2017 prior to the enrollment of the final ninth patient. Eight out of 9 patients completed the final study completion visit. There were no patient discontinuations and/or safety concerns that led to study termination.

Study Design/Methodology

This was an open label, parallel group, partially randomized, single iv LFG316 dose, non-confirmatory study to explore a potential effect of IVIG on the PK and PD of LFG316, from a single site. The study consisted of a screening period of up to approximately 31 days, an optional baseline visit between study Day -21 and Day 1, -6 hour, a Day 1 visit when study medication was administered, a follow up period of 28 days and End of Study (EOS) visit at approximately Day 57. The study investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of LFG316+IVIG and LFG316 alone.

Centers

1 center in 1 country: USA

Objectives:

Primary objective(s)

To evaluate the effect of high-dose IVIG on the single-dose PK of intravenous LFG316 in patients with end-stage renal disease awaiting kidney transplant

Secondary objective(s)

To assess safety and tolerability of LFG316 when administered alone or concomitantly with high-dose IVIG in patients with end-stage renal disease awaiting kidney transplant

Test Product (s), Dose(s), and Mode(s) of Administration
Liquid vial LFG316 infusion

Statistical Methods
Safety: Safety/tolerability data were listed and summarized, without any formal inferential statistical analysis.
Pharmacokinetics: Summary statistics for Cmax, AUClast and AUCinf as primary PK parameters were calculated, λz, tmax, Cmax/D, AUC0-28days, AUC/D, t1/2, MRT, CL, Vss, Vz, were considered as more exploratory.
The primary means of statistical analysis within the study was graphical, using individual patient concentration-time curves identified as being with or without IVIG.

Pharmacodynamics: The analyses for the exploratory objective of exploring PK/PD relationships (including IgG, C5 concentrations, Wieslab results and CH50 levels) were based on the listings and graphs provided: individual LFG316 PK concentrations and time profiles for all subjects; the individual PK parameters listing; listing of total C5 concentrations, Wieslab assay, and CH50.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria
- Adult men or women 18-70 years of age (inclusive) suffering from end-stage renal disease and who were on chronic dialysis therapy.
- Candidates for kidney transplantation who were pre-sensitized and will be undergoing desensitization therapy.
- Written informed consent was obtained before any assessment was performed.
- Able to communicate well with the investigator, to understand and comply with the requirements of the study.
- Recipients who were ABO compatible with donor allograft.
- Patients awaiting kidney allograft from a living or deceased donor. For patients awaiting transplant from a living donor, kidney transplantation was required to occur only after 28 days post LFG316 infusion.
- History of vaccination with meningococcus and pneumococcus between two weeks and 36 months prior to dosing. Documentation was required. If patients had not been vaccinated, they were required to be vaccinated at least 2 weeks prior to

dosing. The choice of vaccine took into account the serotypes prevalent in the geographic areas in which study patients were enrolled.

Exclusion criteria

- Use of other investigational drugs at the time of enrollment, or within five half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever was longer; or longer if required by local regulations.
- Patients with a known contraindication to treatment with blood products.
- Patients with a known pro-thrombotic disorder.
- Patients with a history of thrombosis or hyper-coagulable state, excluding hemodialysis venous access clotting.
- Patients who had positive PCR results for hepatitis B and/or hepatitis C.
- History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
- Patients at risk for tuberculosis (TB), specifically patients who:
  - Had current clinical, radiographic or laboratory evidence of active or latent TB
  - Had a history of active TB
    - Within the last 2 years even if it was treated
    - Greater than 2 years ago, unless there was documentation of adequate treatment according to locally-accepted clinical practice
  - In the opinion of the investigator and based upon an appropriate evaluation, have a risk of reactivation of TB that precludes the use of conventional immunosuppression
- Patients with any severe, progressive or uncontrolled acute or chronic medical condition not related to end stage renal disease (such as uncontrolled infectious disease or sepsis) or clinical laboratory abnormalities at screening or baseline that in the investigator's opinion would make the patient inappropriate for entry into this study.
- Patients requiring or undergoing peritoneal dialysis.
- Patients with known active presence of malignancies.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 50 days after the last dose of LFG316.

Participant Flow Table

Disposition/Reason	LFG316+IVIG combined N=6 n (%)	LFG316 alone N=2 n (%)
SCREENING		
Completed	6 (100)	2 (100)
TREATMENT		
Completed	6 (100)	2 (100)

N = Number of patients entered the EPOCH.

Baseline Characteristics

Characteristic	LFG316+IVIG combined N=6	LFG316 alone N=2
Age (years)		
Mean (SD)	54.7 (5.01)	49.0 (14.14)
Median	54.0	49.0
Range	49 - 61	39 - 59
Sex -n (%)		
Male	4 (66.7)	2 (100)
Female	2 (33.3)	0
Race -n (%)		
Caucasian	2 (33.3)	2 (100)
Black	3 (50.0)	0
Asian	1 (16.7)	0
Ethnicity -n (%)		
Hispanic or Latino	0	2 (100)
Not reported	1 (16.7)	0
Unknown	2 (33.3)	0
Other	3 (50.0)	0
Weight (kg)		
Mean (SD)	84.55 (20.557)	94.80 (21.213)
Median	87.80	94.80
Range	50.8 - 113.3	79.8 - 109.8
Height (cm)		

Mean (SD)	166.58 (15.390)	177.80 (10.748)
Median	165.10	177.80
Range	149.9 - 188.0	170.2 - 185.4
BMI (kg/m2)		
Mean (SD)	30.38 (6.227)	29.75 (3.041)
Median	30.55	29.75
Range	22.6 - 38.2	27.6 - 31.9

Summary of Efficacy

Primary Outcome Result(s)

Summary statistics of LFG316 PK parameter values (PK analysis set)

PK parameter (Unit)	LFG316 + IVIG combined N=6	LFG316 alone N=2	Geometric mean ration (95% CI)
AUC0-28d (d*ug/mL)	3540 ± 502 (14.2%)	5780 ± 1060 (18.4%)	0.612 (0.48, 0.78)
AUCinf (d*ug/mL)	3680 ± 449 (12.2%)	6600 ± 1660 (25.1%)	0.563 (0.44, 0.71)
AUCinf/D (d*ug/mL)	2.28 ± 0.695 (30.5%)	3.47 ± 0.0907 (2.6%)	0.634 (0.42, 0.96)
AUClast (d*ug/mL)	3080 ± 290 (9.4%)	5780 ± 1060 (18.4%)	0.536 (0.45, 0.64)
AUClast/D (d*ug/mL)	1.91 ± 0.555 (29.1%)	3.06 ± 0.132 (4.3%)	0.603 (0.41, 0.89)
CL (L/hr)	0.0196 ± 0.00517 (26.4%)	0.0120 ± 0.000314 (2.6%)	

Cmax (ug/mL)	319 ± 50.7 (15.9%)	367 ± 81.3 (22.2%)	0.871 (0.66, 1.15)
Cmax/D (ug/mL)	0.193 ± 0.0416 (21.5%)	0.193 ± 0.000795 (0.4%)	0.981 (0.72, 1.34)
Lambda Z (1/hr)	0.00279 ± 0.000527 (18.9%)	0.00165 ± 0.000396 (24.0%)	
MRT (hr)	363 ± 62.0 (17.1%)	600 ± 130 (21.7%)	
Tmax (hr)	1.88 (0.233 - 4.00)	2.08 (2.00 - 2.17)	
Vss (L)	7.01 ± 1.84 (26.3%)	7.20 ± 1.37 (19.1%)	
Vz (L)	7.14 ± 2.06 (28.8%)	7.47 ± 1.60 (21.5%)	
T1/2 (hr)	255 ± 43.5 (17.1%)	432 ± 104 (24.0%)	

Statistics for each treatment group are Mean ± SD (CV%) CV% = Coefficient of variation (%) = sd/mean*100; For Tmax, Statistics are Median (Min-Max); Statistics for Treatment comparison column are Geo-mean ratio (90% CI), based on the model for PK parameters.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Primary system organ class	LFG316+IVIG combined N=6 n (%)	LFG316 alone N=2 n (%)	Total N=8 n (%)
Number of patients with at least one AE	4 (66.7)	2 (100)	6 (75.0)
Nervous system disorders	2 (33.3)	1 (50.0)	3 (37.5)
Gastrointestinal disorders	2 (33.3)	0	2 (25.0)
Musculoskeletal and connective tissue disorders	1 (16.7)	1 (50.0)	2 (25.0)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	0	2 (25.0)
Ear and labyrinth disorders	1 (16.7)	0	1 (12.5)
General disorders and administration site conditions	1 (16.7)	0	1 (12.5)
Injury, poisoning and procedural complications	1 (16.7)	0	1 (12.5)
Skin and subcutaneous tissue disorders	1 (16.7)	0	1 (12.5)

Incidence of AEs by Preferred Term n (%)

Preferred term	LFG316+IVIG combined N=6 n (%)	LFG316 alone N=2 n (%)	Total N=8 n (%)
Number of patients with at least one AE	4 (66.7)	2 (100)	6 (75.0)
Pain in extremity	1 (16.7)	1 (50.0)	2 (25.0)
Back pain	1 (16.7)	0	1 (12.5)
Cough	1 (16.7)	0	1 (12.5)
Ear discomfort	1 (16.7)	0	1 (12.5)
Fatigue	1 (16.7)	0	1 (12.5)
Gastrooesophageal reflux disease	1 (16.7)	0	1 (12.5)
Musculoskeletal pain	1 (16.7)	0	1 (12.5)
Nausea	1 (16.7)	0	1 (12.5)
Paraesthesia	1 (16.7)	0	1 (12.5)
Procedural hypotension	1 (16.7)	0	1 (12.5)
Productive cough	1 (16.7)	0	1 (12.5)
Pruritus	1 (16.7)	0	1 (12.5)
Restless legs syndrome	0	1 (50.0)	1 (12.5)
Rhinorrhoea	1 (16.7)	0	1 (12.5)
Skin discolouration	1 (16.7)	0	1 (12.5)
Somnolence	1 (16.7)	0	1 (12.5)

Serious Adverse Events and Deaths

Not applicable.

Other Relevant Findings

Not applicable.

Conclusion:

The iv infusion treatments LFG316 alone and LFG316+IVIG were found to be safe and well tolerated. High dose IVIG infusion administered immediately before infusion of LFG316 has a significant impact on the pharmacokinetics and pharmacodynamics of LFG316 resulting in a shortening of the period in which full inhibition of complement activity can be maintained. The effect of high dose IVIG on LFG316 clearance seems to be most profound during the first 2 weeks approximately after IVIG infusion. Given the 'worst case' scenario with the highest feasible IVIG dose given immediately before LFG316, the effect on clearance of LFG316 or other therapeutic monoclonal antibodies may be reduced by choosing a lower IVIG dose and/or by allowing time between infusion of IVIG and administration of the therapeutic antibody.

Date of Clinical Trial Report

29 June 2018