SDR-CTR-SYN-06

Type of report	Abbreviated
Trial code	HP6015-01
Title of trial	A randomized, single-center, double-blind, placebo- and active-controlled (Part 1) and open-label (Part 2) Phase I trial to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of GRT6015 in healthy male subjects
Brief title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of oral single doses of GRT6015 in healthy men
Trial design	Two-part first-in-human trial: Part 1: randomized, single-site, placebo-controlled, double-blind, oral single dose escalation of GRT6015 in 108 healthy male subjects and including a single-dose, open-label administration of apremilast 30 mg (Otezla®) in 1 trial cohort. Part 2: randomized, single-site, open-label, non-controlled, crossover administration of oral single doses of GRT6015 in 8 healthy male subjects under fasted and fed conditions.
Development phase	Phase I
EudraCT number	2017-000541-40 Universal Trial Number U1111-1192-1860
Investigational medicinal products	• GRT6015 capsules (dose strength 10 mg, 50 mg, 200 mg). • Placebo capsules matching GRT6015 capsules. • Otezla (apremilast 30 mg) film-coated tablets.
Indication	Not applicable
Principal investigator	[redacted], MD Telephone: [redacted]
Trial sites	CRS Clinical Research Services Mannheim GmbH, Clinical Studies Phase I/II, Grenadierstraße 1, 68167 Mannheim, Germany
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	[redacted], PhD (Associate Principal Clinical Pharmacologist) Contact number: [redacted]
Trial period	First subject in: 19 Jul 2017 Last subject out: 01 Sep 2017 Trial suspended: 31 Aug 2017 Early trial termination: 22 May 2018
Product development termination date:	22 May 2018

Trial objectives

Primary objectives:

- Part 1: Safety and tolerability of GRT6015 after an oral single dose escalation.

- Part 2: Pharmacokinetics of GRT6015 after an oral single dose under fasted and fed conditions.

Secondary objectives:

- Part 1: Pharmacokinetics of GRT6015 after an oral single dose escalation; pharmacodynamics of GRT6015 after an oral single dose escalation.
- Part 2: Safety and tolerability of GRT6015 after an oral single dose under fasted and fed conditions.

Trial treatments

Investigational medicinal products (IMPs)

GRT6015 hard gelatin capsules 10 mg (batch PD17002), 50 mg (batch PD17003), 200 mg (batch PD17004), and placebo to GRT6015 hard gelatin capsules (batch PD17001) were manufactured for this trial. All batches had an expiration date of Jan 2018. In addition, Otezla® (apremilast) 30 mg film-coated tablets (batch F2120AE) with an expiry date Oct 2017 were provided to the site.

- GRT6015 capsules were planned to be used for the oral administration of 10, 30, 90, 200, 400, 800, 1400, or 2000 mg in Part 1 (Cohorts 1 to 8). The dose steps could have been adapted by the Benefit-Risk Team (BRT), i.e., dose steps could have been repeated or decreased, compared to the initially planned.
  Administration in Part 2 (Cohort F): The dose for Part 2 was planned to be defined by the BRT, based on the criteria described in in the protocol.
- Placebo capsules matching GRT6015 capsules were planned to be administered orally in Part 1 (Cohorts 1 to 8).
- Otezla (apremilast 30 mg) film-coated tablets were planned to be administered orally in Part 1 (Cohort A).

Summary of the trial procedures and assessments

Part 1 of the trial comprised an Enrollment Visit (within Day -21 to Day -2 before the administration of investigational medicinal product [IMP]), 1 treatment period per cohort (TP1), and a Final Examination between 3 days and 7 days after discharge from the ward. Part 2 of the trial was planned to comprise an Enrollment Visit and 2 treatment periods (TP1 and TP2) followed by a Final Examination.

In Part 1 and Part 2, subjects were planned to be confined to the ward from the morning of Day -1 (i.e., approximately 24 hours prior to the IMP administration) until 72 hours after administration of GRT6015/placebo. After apremilast administration in Part 1, subjects were planned to be confined to the ward for 24 hours.

All IMPs (GRT6015, placebo, or apremilast) were planned to be administered in the morning of the respective dosing day.

Subjects were expected to be in the clinical trial for up to 5 weeks (Part 1) and up to 7 weeks (Part 2).

Trial performance

There was 1 amendment to the protocol before the first subject was enrolled.

The trial was suspended (clinical hold) on 31 Aug 2017 after treatment of Cohorts 1 to 3 in Part 1; it was terminated on 22 May 2018 when the project was stopped for business reasons. Cohorts 4 to 8 (GRT6015/placebo) and Cohort A (apremilast) of Part 1 were not dosed. Part 2 (Cohort F) of the trial was not conducted.

Summary of the statistical methods

Sample size rationale

No formal sample size calculation was performed for this trial. The trial was planned to be conducted in 2 parts, each part being carried out using different subject collectives. In Part 1, each cohort was planned to be made up of 12 subjects; thus, 108 subjects were planned to be allocated to IMP. A sample size of 9 subjects treated with GRT6015 and 3 subjects treated with placebo per cohort was chosen to get a relevant estimate of both the pharmacokinetic and the pharmacodynamic parameters.

In Part 2 of the trial, 8 subjects were planned to be dosed.

A total of 116 subjects was planned to be enrolled. Subjects who discontinued were planned to be replaced in both parts.

Subject populations

- The Enrolled Set comprises all subjects who signed the ICF for the clinical trial.
- The Safety Set includes all subjects with at least 1 IMP administration.
- Part 1: All subjects who had evaluable pharmacokinetic parameters (at least C_{max}) after treatment with GRT6015 were included in the Pharmacokinetic Set (PK Set).
- All subjects who had a measurable baseline (pre-dose) and at least 1 corresponding evaluable tumor necrosis factor alpha (TNFα) assessment in the same treatment period were included in the Pharmacodynamic Set (PD Set).

Statistical methods and analysis

Descriptive statistics:

Descriptive and graphical methods were used in the exploratory data analyses. Analyses mainly considered the PK Set and the Safety Set.

For continuous variables, descriptive statistics and graphical displays of the data were generated as appropriate. Descriptive statistics included various measures of location and variability as appropriate for the analysis, e.g., number of observations, arithmetic mean, standard deviation (SD), minimum, median, and maximum. The geometric mean and geometric coefficient of variation was additionally included in the descriptive analyses of pharmacokinetic parameters, except for time to maximum concentration (t_{max}) and the lag-time observed from dosing to the time point prior to that of the first quantifiable plasma concentration (t_{lag}). For categorical variables, absolute and relative frequencies were presented to summarize the results.

Analysis of the pharmacokinetic parameters:

A statistical analysis was performed to explore dose proportionality of GRT6015. Graphical displays (log-log plots versus dose; including estimated mean slopes) were produced for selected pharmacokinetic parameters.

Analysis of safety parameters:

All safety and tolerability parameters were analyzed descriptively for the Safety Set. All adverse events were summarized with information regarding onset, duration, frequency, intensity, seriousness, relationship to IMP, outcome, and countermeasures taken. Serious adverse events (SAEs) were listed separately. In order to compare a before-and-after effect for laboratory parameters, shift tables with regards to reference ranges were generated for each dose step, and for all subjects.

Analysis of pharmacodynamic parameters:

Ex vivo lipopolysaccharide (LPS)-stimulated TNFα concentrations from blood samples collected pre-dose and after 2, 4, and 10 hours after placebo or GRT6015 administration were descriptively summarized including (percent) change from baseline. The originally planned pharmacometric analyses were not performed.

Summary of results

Subject disposition

A total of 67 male subjects were enrolled and 36 of these subjects were allocated to IMP and treated with a single dose of GRT6015 or placebo. The number of subjects was balanced among the cohorts (12 subjects per cohort: 3 subjects on placebo and 9 subjects on GRT6015). All 36 allocated subjects completed the trial.

Demographics and baseline characteristics

For the Safety Set (36 subjects), the mean (SD) age between treatment groups ranged from 30.4 (7.1) years to 33.8 (7.7) years, mean (SD) height ranged from 174.3 (5.7) cm to 177.8 (4.4) cm, mean (SD) weight ranged from 75.61 (10.16) kg to 79.40 (8.92) kg, and mean (SD) body mass index (BMI) ranged from 24.49 (2.84) kg/m^2 to 25.36 (2.5) kg/m^2. All subjects were 18 years to less than 65 years old. Most subjects (77.78%) were non-smokers.

Safety and tolerability

- There were no deaths and no other SAEs in this trial. No treatment emergent adverse event (TEAE) led to an early discontinuation of a subject from the trial.
- The incidence rates of TEAEs were 11.1% (1 of 9 subjects) in the placebo group and in the GRT6015 30-mg group and 22.2% (2 of 9 subjects) in the GRT6015 10-mg and 90-mg groups.
- Six of 36 subjects (16.7%) experienced 7 TEAEs: diarrhea (1 event), dry mouth (2 events), nasopharyngitis (1 event), and headache (3 events). The events started between 2 hours and 106 hours after IMP administration and were of mild or moderate intensity. The event of nasopharyngitis was reported in a subject in the placebo group and all other under GRT6015 treatment.
- Only headache was reported as TEAE in more than 1 subject (1 subject in the GRT6015 10-mg group and 2 subjects in the GRT6015 90-mg group).
- No clinically relevant effects of GRT6015 on vital signs, body temperature, 12-lead electrocardiogram (ECG), or clinical laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis) were observed.

- Ophthalmologic examinations in an additional follow-up period did not reveal clinically relevant findings.

Pharmacokinetics

Plasma concentrations of GRT6015 indicate a dose-dependent systemic exposure to GRT6015 in Cohorts 1 to 3. The main pharmacokinetic parameters are summarized below and present means (SDs) for the area under the GRT6015 plasma concentration time curves up to the time t (AUC_{0-t}), the maximum plasma concentrations (C_{max}), the time to achieve the maximum plasma concentration (t_{max}), and the elimination half times ($t_{1/2, z}$).

		GRT6015		
Parameter	**(Unit)**	**10 mg**	**30 mg**	**90 mg**
AUC_{0-t}	(h*ng/mL)	45.1 (32.8)	176 (104)	739 (447)
C_{max}	(ng/mL)	9.26 (5.18)	32.5 (22.6)	119 (88.5)
t_{max}	(hours)	2.000 (1.118)	2.111 (0.928)	2.778 (0.972)
$t_{1/2, z}$	(hours)	5.52 (2.43)	8.63 (3.78)	9.56 (3.55)

Pharmacodynamics

A relevant reduction in TNFα release in *ex vivo* LPS-stimulated whole blood samples was observed at 2 hours and 4 hours after the administration of 90 mg of GRT6015.

Conclusions

- Plasma concentrations of GRT6015 following ascending oral single-dose administration of 10, 30, and 90 mg indicate a dose-dependent systemic exposure to GRT6015.
- A relevant reduction in TNFα release in *ex vivo* LPS-stimulated whole blood was observed at the highest administered dose of 90 mg GRT6015.
- GRT6015 single doses of 10, 30, and 90 mg were safe and well tolerated.
  - No dose-dependent adverse event pattern was observed.
  - The observed adverse events were of unspecific nature.
  - Ophthalmologic examinations in an additional follow-up period did not reveal clinically relevant findings.