Clinical trial results:
Safety, tolerability and pharmacokinetics (PKs) of multiple oral doses of GR3027 in healthy male volunteers and single and multiple doses in patients with liver cirrhosis. Preliminary efficacy in cirrhotic patients with evidence of covert hepatic encephalopathy (CHE). A prospective, double-blinded, randomized, placebo-controlled phase I/IIa study.

Summary

EudraCT number	2016-003651-30
Trial protocol	SE DK FI PL HU
Global end of trial date	20 January 2020

Results information

Result version number	v1 (current)
This version publication date	20 November 2020
First version publication date	20 November 2020

Trial information

Trial identification

Sponsor protocol code	UCAB-CT-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Umecrine Cognition AB
Sponsor organisation address	Fogdevreten 2, Solna, Sweden, SE-171 65
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and tolerability of GR3027 after multiple dose administration in healthy male volunteers and after single and multiple dose administration in cirrhotic patients.

General information
The study consisted of 4 separate parts:

A Multiple Ascending Dose (MAD) in healthy subjects for safety and PK.
B Single dose in cirrhotic patients Child-Pugh class B for safety, PK and preliminary assessment of EEG findings.
C MAD in cirrhotic patients Child-Pugh class A and B for safety and PK and preliminary assessment of EEG findings.
D Extended treatment (21 consecutive days) in cirrhotic patients Child-Pugh class A and B with manifestation of CHE for safety and preliminary efficacy.

A 4-weeks screening period was applied.
In Part A, 5 QD (1st cohort) or 5 BID (2nd and 3rd cohorts) doses were given. In Part C, 5 BID doses were given in all cohorts. In Part D, 21 BID doses were given in all cohorts.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonization (ICH)/Good Clinical Practice (GCP) E6 (R1), European Union (EU) Clinical Trials Directive, and applicable local regulatory requirements. In accordance with the EU Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the study.

A pre-defined dosing strategy was applied in the trial, including evaluations of an Internal Safety Review Committee (iSRC), before proceeding to the next cohort or trial part.

In parts A and C of the trial, each cohort were divided into at least 3 groups (2+3+3).The subjects remained in the research clinic from the evening before first dosing (Day -1) until 48 h post last dose (Day 3 and Day 7, respectively) and were closely monitored by medical staff. Each group was dosed approximately 48 hours apart. In each group, the subjects/patients were dosed with an interval of at least 90 min between subjects.

In each cohort of Part B (single dose, cirrhotic patients) a "sentinel group" of 2 subjects (1 GR3027/1 placebo) was dosed first and closely observed for 48 h before proceeding to dose the remaining subjects with an interval of at least 24 h between subjects.

A summary of the safety and PK results from Parts A and B was submitted to the Swedish Competent Authority and the IEC for approval before initiating Parts C and D.

In each cohort of Part C (MAD, cirrhotic patients) a "sentinel group" of 2 subjects (1 GR3027/1 placebo) was dosed first and closely observed for 48 h before proceeding to dose the remaining subjects.

In Part D (extended treatment, cirrhotic patients) the morning doses on Days 1, 10 and 21 were administered under surveillance.

No DLTs, as defined in the Clinical Study Protocol Section 9.1.1.2, occurred.

Background therapy:

In Parts B-D, treatments with lactulose, rifaximin, proton-pump inhibitors (PPIs), diuretics, anti-epileptics, sleep aids, and selective serotonin reuptake inhibitor (SSRI) were allowed, but must be stable during the trial, except for adjustment of lactulose dose (e.g. for diarrhoea).

Evidence for comparator:

This was a placebo-controlled trial vs investigational drug.

No other comparators were used.

Abbreviations used:
AE: Adverse event
ANT1: Animal Naming Test
BID: Twice daily
CHE: Covert hepatic encephalopathy
CTCAE: Common Terminology Criteria for Adverse Events
HE: Hepatic encephalopathy
DTABR: Ratio relative powers of delta and theta to the relative powers of alpha and beta
IMP: Investigational medicinal product
MAD: Multiple ascending dose
MDF: Mean dominant frequency
OHE: Overt hepatic encephalopathy
PK: Pharmacokinetic
PPASC: Per protocol analysis set, Part C
PPASD: Per protocol analysis set, Part D
QD: Once daily
QoL: Quality of life
SAE: Serious adverse event
SD: Single dose
TEAE: Treatment emergent adverse event

Actual start date of recruitment	16 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Sweden: 37
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Hungary: 32
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Ukraine: 8
Worldwide total number of subjects	101
EEA total number of subjects	71

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	86
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part A: The healthy subjects were recruited from a register of healthy volunteers at the Swedish CRO CTC and from advertising in media.
Part B-D: Cirrhotic patients were recruited from a network of referring clinics.
1 subject from Part B participated also in Part C.
5 subjects from Part C participated also in Part D.

Pre-assignment

Screening details:

Consenting subjects were screened for eligibility to study Parts A to D, according to study-specific inclusion/exclusion criteria within 4 weeks prior to the first administration of IMP. Eligible subjects were randomized on Day 1 to receive either GR3027 or placebo and consecutively included in one of the cohorts in applicable study part.

Period 1

Period 1 title	Overall Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Capsules of GR3027 and placebo were of identical appearance.
The IMP dispensing was performed according to the randomisation scheme by 2 un-blinded staff, not involved in the conduct of the study.
In Parts A-C, the IMP was administered by blinded study staff at the research clinic. In Part D, the IMP was self-administered by the subjects.
A code breaking procedure was available in the eCRF system Viedoc™ with an audit trail. No un-blinding occurred in the study prior to database closure.

Arms

Are arms mutually exclusive?	No
Arm title	Part A, A1 50 mg QD

Arm description:

Healthy male subjects recieved an oral dose of 50 mg GR3027 QD for 5 days.

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

5 GR3027 10 mg orange hard gelatine capsules were administered QD

Arm title	Part A, A2 50 mg BID (100 mg per day)

Arm description:

Healthy male subjects recieved oral doses of 50 mg GR3027 BID for 5 days.

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

5 GR3027 10 mg orange hard gelatine capsules were administered BID

Arm title	Part A, A3 100 mg BID (200 mg per day)

Arm description:

Healthy male subjects recieved oral doses of 100 mg GR3027 BID for 5 days.

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

10 GR3027 10 mg orange hard gelatine capsules were administered BID

Arm title	Part A, Placebo

Arm description:

Healthy male subjects recieved placebo capsules QD (cohort A1) or BID (cohorts A2-A3) for 5 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules, with identical appearence to the GR3027 capsules, were administered in a number matching the dose of the active drug

Arm title	Part B, 10 mg SD

Arm description:

Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of 10 mg GR3027

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1 GR3027 10 mg orange hard gelatine capsule was administered as a single dose

Arm title	Part B, Placebo

Arm description:

Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

A placebo capsule, with identical appearence to the GR3027 capsules, were administered as a single dose

Arm title	Part C, C1 10 mg BID (20 mg per day)
Arm description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 5 days	
Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
1 GR3027 10 mg orange hard gelatine capsule was administered BID	
Arm title	Part C, C2 40 mg BID (80 mg per day)
Arm description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 5 days	
Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
4 GR3027 10 mg orange hard gelatine capsules was administered BID	
Arm title	Part C, C3 80 mg BID (160 mg per day)
Arm description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 5 days	
Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
8 GR3027 10 mg orange hard gelatine capsules was administered BID	
Arm title	Part C, Placebo
Arm description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 5 days.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Placebo capsules, with identical appearence to the GR3027 capsules, were administered in a number matching the dose of the active drug	
Arm title	Part D, D1 10 mg BID (20 mg per day)
Arm description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 21 days	
Arm type	Experimental

Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1 GR3027 10 mg orange hard gelatine capsule was administered BID

Arm title	Part D, D2 40 mg BID (80 mg per day)

Arm description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 21 days

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4 GR3027 10 mg orange hard gelatine capsules was administered BID

Arm title	Part D, D3 80 mg BID (160 mg per day)

Arm description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 21 days

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

8 GR3027 10 mg orange hard gelatine capsules was administered BID

Arm title	Part D, Placebo

Arm description:

Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 21 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo capsules, with identical appearence to the GR3027 capsules, were administered in a number matching the dose of the active drug

Arm title	Part D, Total (D1+D2+D3)

Arm description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10, 40, or 80 mg GR3027 BID for 21 days

Arm type	Experimental
Investigational medicinal product name	GR3027 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1, 4, or 8 GR3027 10 mg orange hard gelatine capsules were administered BID

Number of subjects in period 1	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part A, Placebo	Part B, 10 mg SD	Part B, Placebo
Started	6	6	2
Completed	6	6	2
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part C, Placebo	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)
Started	6	10	10
Completed	6	9	10
Not completed	0	1	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo	Part D, Total (D1+D2+D3)
Started	13	12	33
Completed	11	12	30
Not completed	2	0	3
Consent withdrawn by subject	1	-	1

Adverse event, non-fatal	1	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Part A, A1 50 mg QD
Reporting group description:	
Healthy male subjects recieved an oral dose of 50 mg GR3027 QD for 5 days.	
Reporting group title	Part A, A2 50 mg BID (100 mg per day)
Reporting group description:	
Healthy male subjects recieved oral doses of 50 mg GR3027 BID for 5 days.	
Reporting group title	Part A, A3 100 mg BID (200 mg per day)
Reporting group description:	
Healthy male subjects recieved oral doses of 100 mg GR3027 BID for 5 days.	
Reporting group title	Part A, Placebo
Reporting group description:	
Healthy male subjects recieved placebo capsules QD (cohort A1) or BID (cohorts A2-A3) for 5 days.	
Reporting group title	Part B, 10 mg SD
Reporting group description:	
Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of 10 mg GR3027	
Reporting group title	Part B, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of placebo	
Reporting group title	Part C, C1 10 mg BID (20 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 5 days	
Reporting group title	Part C, C2 40 mg BID (80 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 5 days	
Reporting group title	Part C, C3 80 mg BID (160 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 5 days	
Reporting group title	Part C, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 5 days.	
Reporting group title	Part D, D1 10 mg BID (20 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 21 days	
Reporting group title	Part D, D2 40 mg BID (80 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 21 days	
Reporting group title	Part D, D3 80 mg BID (160 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 21 days	
Reporting group title	Part D, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 21 days.	
Reporting group title	Part D, Total (D1+D2+D3)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10, 40, or 80 mg GR3027 BID for 21 days	

Reporting group values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)
Number of subjects	6	6	6
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	33.33	31.33	32.00
standard deviation	± 6.80	± 7.63	± 8.67
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	6	6	6

Reporting group values	Part A, Placebo	Part B, 10 mg SD	Part B, Placebo
Number of subjects	6	6	2
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	28.50	63.50	58.50
standard deviation	± 4.04	± 2.07	± 4.95
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	6	6	2

Reporting group values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Number of subjects	6	6	6

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	54.7	55.0	50.2
standard deviation	± 10.3	± 9.8	± 11.9
Gender categorical Units: Subjects			
Female	1	1	1
Male	5	5	5

Reporting group values	Part C, Placebo	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)
Number of subjects	6	10	10
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	60.5	53.0	53.2
standard deviation	± 5.5	± 6.8	± 12.9
Gender categorical Units: Subjects			
Female	4	4	3
Male	2	6	7

Reporting group values	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo	Part D, Total (D1+D2+D3)
Number of subjects	13	12	33
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	56.3	59.7	54.4
standard deviation	± 12.2	± 9.4	± 10.9
Gender categorical Units: Subjects			
Female	4	5	11
Male	9	7	22

Reporting group values	Total		
Number of subjects	101		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	23		
Male	78		

End points

End points reporting groups

Reporting group title	Part A, A1 50 mg QD
Reporting group description:	
Healthy male subjects recieved an oral dose of 50 mg GR3027 QD for 5 days.	
Reporting group title	Part A, A2 50 mg BID (100 mg per day)
Reporting group description:	
Healthy male subjects recieved oral doses of 50 mg GR3027 BID for 5 days.	
Reporting group title	Part A, A3 100 mg BID (200 mg per day)
Reporting group description:	
Healthy male subjects recieved oral doses of 100 mg GR3027 BID for 5 days.	
Reporting group title	Part A, Placebo
Reporting group description:	
Healthy male subjects recieved placebo capsules QD (cohort A1) or BID (cohorts A2-A3) for 5 days.	
Reporting group title	Part B, 10 mg SD
Reporting group description:	
Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of 10 mg GR3027	
Reporting group title	Part B, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of placebo	
Reporting group title	Part C, C1 10 mg BID (20 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 5 days	
Reporting group title	Part C, C2 40 mg BID (80 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 5 days	
Reporting group title	Part C, C3 80 mg BID (160 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 5 days	
Reporting group title	Part C, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 5 days.	
Reporting group title	Part D, D1 10 mg BID (20 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 21 days	
Reporting group title	Part D, D2 40 mg BID (80 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 21 days	
Reporting group title	Part D, D3 80 mg BID (160 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 21 days	
Reporting group title	Part D, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 21 days.	
Reporting group title	Part D, Total (D1+D2+D3)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10, 40, or 80 mg GR3027 BID for 21 days	

Primary: Safety as number of subjects with adverse events

End point title	Safety as number of subjects with adverse events[1][2]

End point description:

Safety was assessed by occurrence and frequency of AEs, changes in laboratory parameters, vital signs, ECG, and physical examination. Medically important abnormalities observed in laboratory parameters, vital signs, ECG, and physical examinations were reported as adverse events.
AEs occurring before first administration of IMP were defined as baseline events. AEs starting from first administration of IMP were defined as TEAEs.
The grading of the severity of AEs followed the CTCAE v4.03. The CTCAE displays severity Grades 1 through 5.

End point type	Primary

End point timeframe:

From signing of informed consent and until follow-up assessments, 21 days after the last dose.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In this trial, safety was the primary endpoint. In accordance with the trial protocol no statistical analysis was performed, but data were presented as an overview of all subjects with AEs including severity, relationship to the IP, and SAEs.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The Arm Total (D1+D2+D3+D4¤) is a combination of the arms in Part D and is not relevant for this endpoint. Safety data are reported for the arms D1-D4 separately.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	Part A, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: Subjects with adverse events				
Any AE	5	3	4	2
Any SAE	0	0	0	0
Any baseline event	2	1	2	0
Any TEAE	4	2	4	2
Not related TEAEs	2	1	2	2
Possibly related TEAEs	3	1	3	2
Probably related TEAEs	0	0	2	1
TEAEs of Grade 1 severity	4	2	4	2
TEAEs of Grade 2 severity	0	0	1	0
TEAEs of Grade 3 severity	0	0	0	0
TEAEs of Grade 4 severity	0	0	0	0
TEAEs of Grade 5 severity	0	0	0	0

End point values	Part B, 10 mg SD	Part B, Placebo	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	6	6
Units: Subjects with adverse events				
Any AE	3	1	3	4
Any SAE	0	0	0	0

Any baseline event	2	0	0	1
Any TEAE	3	1	3	3
Not related TEAEs	3	1	1	0
Possibly related TEAEs	0	0	2	2
Probably related TEAEs	0	0	0	1
TEAEs of Grade 1 severity	3	1	3	3
TEAEs of Grade 2 severity	0	0	0	0
TEAEs of Grade 3 severity	0	0	0	0
TEAEs of Grade 4 severity	0	0	0	0
TEAEs of Grade 5 severity	0	0	0	0

End point values	Part C, C3 80 mg BID (160 mg per day)	Part C, Placebo	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	10	10
Units: Subjects with adverse events				
Any AE	1	1	3	3
Any SAE	0	0	0	0
Any baseline event	0	1	1	0
Any TEAE	1	0	2	3
Not related TEAEs	1	0	2	0
Possibly related TEAEs	0	0	0	3
Probably related TEAEs	0	0	0	0
TEAEs of Grade 1 severity	0	0	2	3
TEAEs of Grade 2 severity	1	0	0	1
TEAEs of Grade 3 severity	0	0	0	0
TEAEs of Grade 4 severity	0	0	0	0
TEAEs of Grade 5 severity	0	0	0	0

End point values	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	12		
Units: Subjects with adverse events				
Any AE	6	5		
Any SAE	1	0		
Any baseline event	1	2		
Any TEAE	6	4		
Not related TEAEs	5	2		
Possibly related TEAEs	3	2		
Probably related TEAEs	2	0		
TEAEs of Grade 1 severity	5	3		
TEAEs of Grade 2 severity	1	2		
TEAEs of Grade 3 severity	1	0		
TEAEs of Grade 4 severity	0	0		
TEAEs of Grade 5 severity	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Lambdaz after first dose

End point title	Part A: PK - Lambdaz after first dose[3]

End point description:

Plasma terminal elimination rate constant

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5[4]	
Units: /h				
median (full range (min-max))	0.0650 (0.047 to 0.134)	0.1425 (0.103 to 0.186)	0.1401 (0.061 to 0.195)	

Notes:

[4] - For 1 subject in dose group 100 mg BID, Lambdaz could not be calculated following the first dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - T1/2 after first dose

End point title	Part A: PK - T1/2 after first dose[5]

End point description:

Plasma Terminal half-life

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.

Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5[6]	
Units: hour				
median (full range (min-max))	10.8237 (5.168 to 14.628)	4.9197 (3.724 to 6.758)	4.9477 (3.556 to 11.315)	

Notes:

[6] - For 1 subject in dose group 100 mg BID, T1/2 could not be calculated following the first dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Tmax after first dose

End point title	Part A: PK - Tmax after first dose[7]

End point description:

Time to maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (full range (min-max))	1.5000 (1.033	1.2500 (1.000	1.7500 (1.500	

to 2.033)	to 2.000)	to 6.000)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Cmax after first dose

End point title	Part A: PK - Cmax after first dose[8]

End point description:

Maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: ng/mL				
median (full range (min-max))	740.00 (638.0 to 990.0)	929.00 (700.0 to 1150.0)	1395.00 (595.0 to 1750.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - AUC(0-t) after first dose

End point title	Part A: PK - AUC(0-t) after first dose[9]

End point description:

Area under the plasma concentration time curve to last nonzero concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post

first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: h*ng/mL				
median (full range (min-max))	3926.2 (2993 to 5397)	3415.4 (2546 to 4283)	5823.0 (5374 to 7816)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - AUCinf after first dose

End point title	Part A: PK - AUCinf after first dose[10]

End point description:

Area under the plasma concentration time curve to infinity (observed value)

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5[11]	
Units: h*ng/mL				
median (full range (min-max))	4785.5 (3093 to 6219)	4059.1 (3112 to 5603)	7400.0 (6887 to 9705)	

Notes:

[11] - For 1 subject in dose group 100 mg BID, AUCinf could not be calculated following the first dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Vz/F after first dose

End point title	Part A: PK - Vz/F after first dose[12]

End point description:

Volume of distribution

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5[13]	
Units: litre				
median (full range (min-max))	158.9 (90 to 185)	80.9 (72 to 111)	96.5 (69 to 169)	

Notes:

[13] - For 1 subject in dose group 100 mg BID, Vz/F could not be calculated following the first dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - CL/F after first dose

End point title	Part A: PK - CL/F after first dose[14]

End point description:

Total apparent clearance of drug from plasma/serum

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose, 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	5[15]	
Units: L/h				
median (full range (min-max))	10.4 (8 to 16)	12.4 (9 to 16)	13.5 (10 to 15)	

Notes:

[15] - For 1 subject in dose group 100 mg BID, Cl/F could not be calculated following the first dose.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Ae after first dose

End point title	Part A: PK - Ae after first dose[16]

End point description:

Urine recovery of GR3027

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter Urine recovery (Ae) was only measured in Part A of the trial.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	6	6	
Units: µg				
median (full range (min-max))	(to)	2.31 (0.0 to 20.1)	16.92 (0.0 to 48.5)	

Notes:

[17] - For the first dose in group 50 mg QD, assessment of Ae was not performed due to analytical problems.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Fe after first dose

End point title	Part A: PK - Fe after first dose[18]

End point description:

Fraction of the dose excreted in urine for GR3027

End point type	Secondary

End point timeframe:

Predose to 24 h for dose group 50mg QD.
Predose to 12 h for dose group 50mg BID and 100 mg BID.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter Fraction of dose extracted in urine (Fe) was only measured in Part A of the trial.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	6	6	
Units: percent (%)				
median (full range (min-max))	(to)	0.0046 (0.000 to 0.040)	0.0169 (0.000 to 0.049)	

Notes:

[19] - For the first dose in group 50 mg QD, assessment of Fe was not performed due to analytical problems.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Lambdaz after last dose

End point title	Part A: PK - Lambdaz after last dose[20]

End point description:

Plasma terminal elimination rate constant

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: /h				
median (full range (min-max))	0.0619 (0.055 to 0.135)	0.0613 (0.040 to 0.087)	0.0639 (0.035 to 0.090)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - T1/2 after last dose

End point title	Part A: PK - T1/2 after last dose[21]

End point description:

Plasma terminal half-life

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (full range (min-max))	11.2292 (5.117 to 12.623)	11.6258 (7.930 to 17.248)	10.9620 (7.703 to 19.723)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Tmax after last dose

End point title	Part A: PK - Tmax after last dose[22]

End point description:

Time to maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (full range (min-max))	1.7500 (1.000 to 2.000)	1.5000 (1.000 to 4.000)	2.5000 (2.000 to 4.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Cmax, ss, after last dose

End point title	Part A: PK - Cmax, ss, after last dose[23]

End point description:

Maximum plasma concentration at steady-state

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.

Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: ng/mL				
median (full range (min-max))	848.50 (705.0 to 1190.0)	870.50 (595.0 to 1350.0)	1365.00 (1300.0 to 1850.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Cmin, ss, after last dose

End point title	Part A: PK - Cmin, ss, after last dose[24]

End point description:

Minimum plasma concentration at steady-state

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: ng/mL				
median (full range (min-max))	64.25 (16.9 to 86.7)	204.00 (147.0 to 409.0)	455.00 (312.0 to 825.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Vz/F after last dose

End point title	Part A: PK - Vz/F after last dose[25]

End point description:

Volume of distribution for dose interval

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: litre(s)				
median (full range (min-max))	145.5 (72 to 176)	148.3 (123 to 234)	322.9 (215 to 591)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - % fluctuation after last dose

End point title	Part A: PK - % fluctuation after last dose[26]

End point description:

Peak trough fluctuation within one dosing interval at steady state

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: percent (%)				
median (full range (min-max))	402.43 (285.4 to 471.9)	165.28 (113.3 to 207.4)	120.00 (48.7 to 204.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - AUC over dosing interval after last dose, and dose proportionality

End point title	Part A: PK - AUC over dosing interval after last dose, and dose proportionality[27]

End point description:

Area under the plasma concentration time curve over dosing interval

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Group A1 (50 mg QD): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post last dose.
Groups A2 and A3 (50 mg BID and 100 mg BID): Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

Dose proportionality given in attached Table 12.1.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: h*ng/mL				
median (full range (min-max))	5400.6 (3627 to 5929)	4548.2 (4062 to 8207)	9337.2 (8629 to 12927)	

Attachments (see zip file)	Table 12.1 Dose proportionalty/Table 12.1 Dose

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Ae after last dose

End point title	Part A: PK - Ae after last dose[28]
End point description:	
Urine recovery of GR3027	
End point type	Secondary
End point timeframe:	
Predose to 24h post last dose.	

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter Urine recovery (Ae) was only measured in Part A of the trial.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[29]	6	6	
Units: µg				
median (full range (min-max))	19.00 (0.0 to 30.6)	0.00 (0.0 to 29.8)	45.00 (24.6 to 63.5)	

Notes:

[29] - For the last dose in group 50 mg QD, complete assessment of Ae was performed for 3 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Fe after last dose

End point title	Part A: PK - Fe after last dose[30]
End point description:	
Fraction of the dose excreted in urine for GR3027	
End point type	Secondary
End point timeframe:	
Predose to 24 h post last dose.	

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter Fraction of dose extracted in urine (Fe) was only measured in Part A of the trial.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[31]	6	6	
Units: percent (%)				
median (full range (min-max))	0.0380 (0.000 to 0.061)	0.0000 (0.000 to 0.060)	0.0450 (0.025 to 0.063)	

Notes:

[31] - For the last dose in group 50 mg QD, complete assessment of Fe was performed for 3 subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Accumulation ratio, Cmax, after last dose

End point title	Part A: PK - Accumulation ratio, Cmax, after last dose[32]

End point description:

Accumulation ratio for Cmax between first and last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: no unit				
median (full range (min-max))	1.14 (1.00 to 1.32)	0.93 (0.79 to 1.57)	1.03 (0.78 to 2.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: PK - Accumulation ratio, AUC, after last dose

End point title	Part A: PK - Accumulation ratio, AUC, after last dose[33]

End point description:

Accumulation ratio for AUC between first and last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

End point values	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: no unit				
median (full range (min-max))	1.23 (1.10 to 1.42)	1.34 (1.28 to 1.98)	1.54 (1.32 to 2.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - Lambdaz after first dose

End point title	Parts B and C: PK - Lambdaz after first dose[34]

End point description:

Plasma terminal elimination rate constant

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

Due to a short PK sampling interval on Day 1 (0-12h), calculated values for Lambdaz are uncertain for Day 1 in Part C.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: /h				
median (full range (min-max))	0.0522 (0.021 to 0.058)	0.0778 (0.061 to 0.169)	0.0791 (0.062 to 0.129)	0.0827 (0.062 to 0.099)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - T1/2 after first dose

End point title	Parts B and C: PK - T1/2 after first dose[35]

End point description:

Plasma terminal half-life

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

Due to a short PK sampling interval on Day 1 (0-12h), calculated values for T1/2 are uncertain for Day 1 in Part C.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hour				
median (full range (min-max))	13.2789 (11.936 to 32.925)	8.9314 (4.106 to 11.398)	8.7809 (5.374 to 11.227)	8.3816 (6.975 to 11.123)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - Tmax after first dose

End point title	Parts B and C: PK - Tmax after first dose[36]

End point description:

Time to maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hour				
median (full range (min-max))	0.8500 (0.667 to 1.017)	1.000 (0.33 to 3.00)	1.000 (0.67 to 2.00)	1.515 (1.00 to 2.85)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - Cmax after first dose

End point title	Parts B and C: PK - Cmax after first dose[37]

End point description:

Maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL				
median (full range (min-max))	107.50 (80.1 to 116.0)	109.25 (53.9 to 262.0)	467.50 (289.0 to 833.0)	861.00 (462.0 to 1260.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - AUC(0-t) after first dose

End point title	Parts B and C: PK - AUC(0-t) after first dose[38]

End point description:

Area under the plasma concentration time curve

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10 mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: h*ng/mL				
median (full range (min-max))	740.6 (628 to 1319)	394.09 (292.9 to 616.5)	1944.75 (1247.0 to 3008.0)	3792.25 (2762.5 to 6012.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - AUCinf after first dose

End point title	Parts B and C: PK - AUCinf after first dose[39]

End point description:

Area under the plasma concentration time curve, predicted to infinity

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

Due to a short PK sampling interval on Day 1 (0-12h), calculated values for AUCinf are uncertain for Day 1 in Part C.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: h*ng/mL				
median (full range (min-max))	1114.8 (830 to 1951)	600.23 (362.6 to 964.2)	2954.32 (1754.8 to 4988.8)	5822.83 (4952.5 to 9756.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - Vz/F after first dose

End point title	Parts B and C: PK - Vz/F after first dose[40]

End point description:

Volume of distribution

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

Due to a short PK sampling interval on Day 1 (0-12h), calculated values for Vz/F are uncertain for Day 1 in Part C.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: litre(s)				
median (full range (min-max))	214.0 (157 to 243)	181.25 (137.2 to 296.2)	183.86 (99.0 to 304.4)	154.25 (101.2 to 237.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - CL/F after first dose

End point title	Parts B and C: PK - CL/F after first dose[41]

End point description:

Total apparent clearance of drug from plasma/serum

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points.
Part B: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, and 48 hours post first dose.
Part C: Predose , 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post first dose.

Due to a short PK sampling interval on Day 1 (0-12h), calculated values forCL/F are uncertain for Day 1 in Part C.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: L/h				
median (full range (min-max))	9.0 (5 to 12)	16.77 (10.3 to 27.4)	13.44 (8.2 to 22.8)	13.80 (8.2 to 16.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Parts B and C: PK - Fraction unbound after first dose

End point title	Parts B and C: PK - Fraction unbound after first dose[42]

End point description:

The fraction of drug in serum that is not bound to a carrier protein or other molecule.

End point type	Secondary

End point timeframe:

Predose to 48 h for dose group B, 10 mg.
Predose to 12 h for dose groups C1, 10mg BID; C2, 40 mg BID; and C3, 80 mg BID.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The parameter fraction unbound was only measured in Trial parts B and C, why no values are available for parts A or D.

End point values	Part B, 10 mg SD	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4[43]	6	6
Units: percent (%)				
median (full range (min-max))	0.966 (0.72 to 1.08)	0.76340 (0.6873 to 0.9713)	0.69550 (0.5613 to 1.6230)	0.91955 (0.6455 to 1.9155)

Notes:

[43] - For 2 subjects in the 10 mg BID group, data on unbound drug conc were missing at all timepoints.

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Lambdaz after last dose

End point title	Part C: PK - Lambdaz after last dose[44]

End point description:

Plasma terminal elimination rate constant

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: /h				
median (full range (min-max))	0.0465 (0.038 to 0.108)	0.0515 (0.026 to 0.087)	0.0481 (0.019 to 0.066)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - T1/2 after last dose

End point title	Part C: PK - T1/2 after last dose[45]

End point description:

Plasma terminal half-life

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (full range (min-max))	14.9476 (6.440 to 18.475)	13.4681 (7.970 to 26.626)	14.5413 (10.553 to 37.362)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Tmax after last dose

End point title	Part C: PK - Tmax after last dose[46]

End point description:

Time to maximum plasma concentration

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: hour				
median (full range (min-max))	2.50 (1.0 to 4.0)	1.50 (1.0 to 4.0)	1.00 (1.0 to 3.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Cmax after last dose, and dose proportionality

End point title	Part C: PK - Cmax after last dose, and dose proportionality[47]

End point description:

Maximum plasma concentration at steady-state

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

Dose proportionality given in attached Table 14.61.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.

Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: ng/mL				
median (full range (min-max))	101.80 (64.5 to 158.0)	473.5 (197.0 to 699.0)	1470.0 (610.0 to 1820.0)	

Attachments (see zip file)	Dose proportionalty Cmax/Table 14.61 Dose

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - AUCinf after last dose

End point title	Part C: PK - AUCinf after last dose[48]

End point description:

Area under the plasma concentration time curve, predicted to infinity

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: h*ng/mL				
median (full range (min-max))	1897.90 (618.5 to 4096.3)	8340.95 (3818.8 to 16127.8)	20501.200 (9787.0 to 59817.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - AUC(% Extrapolation) after last dose

End point title	Part C: PK - AUC(% Extrapolation) after last dose[49]

End point description:

Area under the plasma concentration time curve, % extrapolation

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: percent (%)				
median (full range (min-max))	24.694 (8.41 to 32.92)	7.619 (1.65 to 28.18)	9.328 (4.20 to 42.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Cmin after last dose

End point title	Part C: PK - Cmin after last dose[50]

End point description:

Minimum plasma concentration at steady-state

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: ng/mL				
median (full range (min-max))	42.35 (14.2 to 83.2)	203.50 (89.3 to 278.0)	449.50 (239.0 to 824.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - % fluctuation after last dose

End point title	Part C: PK - % fluctuation after last dose[51]

End point description:

Peak trough fluctuation within one dosing interval at steady state.

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: percent (%)				
median (full range (min-max))	101.6 (28.7 to 165.1)	91.85 (57.4 to 158.0)	107.31 (27.6 to 206.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Vz/F after last dose

End point title	Part C: PK - Vz/F after last dose[52]

End point description:

Volume of distribution for dose interval

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-

points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: litre(s)				
median (full range (min-max))	255.21 (191.6 to 403.0)	273.66 (101.9 to 408.1)	243.85 (100.0 to 407.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - AUC over dosing interval after last dose and dose proportionality

End point title	Part C: PK - AUC over dosing interval after last dose and dose proportionality[53]

End point description:

Area under the plasma concentration time curve over the dosing interval

Venous blood samples for the determination of GR3027 in plasma were collected at pre-specified time-points: Predose Day 5 (last dose), 20, 40, 60, 90, 120, 180 min, 4, 6, 9, 12, 18, 24, 36, and 48 hours post last dose.

Dose proportionality given in attached Table 14.60.

End point type	Secondary

End point timeframe:

Predose Day 5 (last dose) to 48 h post last dose.

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: h*ng/mL				
median (full range (min-max))	763.35 (428.6 to 1162.3)	3843.09 (1864.1 to 4514.8)	8922.97 (4934.3 to 13227.6)	

Attachments (see zip file)	Dose proportionalty AUC/Table 14.60 Dose

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Accumulation ratio, Cmax, after last dose

End point title	Part C: PK - Accumulation ratio, Cmax, after last dose[54]

End point description:

Accumulation ratio for Cmax between first and last dose

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: no unit				
median (full range (min-max))	0.85 (0.42 to 2.00)	1.15 (0.55 to 1.40)	1.96 (0.48 to 2.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part C: PK - Accumulation ratio, AUC, after last dose

End point title	Part C: PK - Accumulation ratio, AUC, after last dose[55]

End point description:

Accumulation ratio for AUC between first and last dose.

End point type	Secondary

End point timeframe:

Predose to 48 h post last dose.

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics for Part A (healthy volunteers) are reported in separate endpoints as the results are not comparable to PK results in cirrhotic patients.
Only 1 dose was given in Part B
No pharmacokinetic parameters but exposure were calculated for Part D.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	6	
Units: no unit				
median (full range (min-max))	1.84 (1.46 to 2.29)	1.68 (1.41 to 2.51)	2.06 (1.37 to 3.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part D: PK - Exposure

End point title	Part D: PK - Exposure[56]

End point description:

Exposure as plasma concentration at Day 1 (predose), Day 10 (predose), Day 21 (predose).
A 12 h post last dose sample on Day 21 in dose groups D2 and D3 should be collected if accepted by the subject, but only 1 subject agreed and data are not shown for this time point.

End point type	Secondary

End point timeframe:

Predose Day 1 to 12 h post last dose (Day 21).

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The PK parameter Exposure was only calculated for Part D of the trial.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10[57]	10	12[58]	
Units: ng/mL				
median (full range (min-max))				
Day 1, predose	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	
Day 10, predose	69.10 (15.3 to 120.0)	186.50 (54.9 to 448.0)	416.50 (182.0 to 716.0)	
Day 21, predose	42.75 (0.0 to 94.4)	146.50 (42.0 to 189.0)	465.00 (0.0 to 582.0)	

Notes:

[57] - On Day 10, samples were collected from only 9 subjects,

[58] - On Day 10, samples were collected from only 11 subjects,

Statistical analyses

No statistical analyses for this end point

Secondary: Part C, Change in EEG parameters (MDF) from baseline

End point title	Part C, Change in EEG parameters (MDF) from baseline[59]

End point description:

Change from baseline in EEG parameters: Mean Dominant Frequency, MDF-US (average of T3-O1 and T4-O2) (PPASC).

The data are presented by "Dose group" (Per dose group overall, all timepoints), by timepoint (each specific time-point from all 5 days combined), by day (all time-points a specific day combined, "Post-dose" is combined Day 1 data), and by Days 2-5 combined (= After Day 1).
Change from pre-dose at consecutive days has been evaluated (using MMRM). Using the least square mean estimate, no statistically significant difference from placebo was achieved.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 5, 8 hours post dose

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.
In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented.
In Part D of the trial (extended treatment), different measurement timepoints were used and EEG data for Part D are described in separate endpoints.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	Part C, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: Hz				
least squares mean (confidence interval 95%)				
Dose group	-0.2694 (-1.2323 to 0.6935)	-0.3911 (-1.3474 to 0.5652)	-0.1494 (-1.0905 to 0.7917)	-0.6181 (-1.65167 to 0.4154)
Post-dose	-0.3073 (-1.2746 to 0.6600)	-0.3640 (-1.3242 to 0.5963)	-0.2184 (-1.1632 to 0.7265)	-0.5733 (-1.6110 to 0.4644)
90 min	-0.0730 (-1.0857 to 0.9398)	-0.3878 (-1.3917 to 0.6161)	-0.0819 (-1.0716 to 0.9079)	-0.6135 (-1.6934 to 0.4664)
180 min	-0.2018 (-1.2115 to 0.8080)	-0.3953 (-1.3992 to 0.6086)	-0.0400 (-1.0266 to 0.9465)	-0.6350 (-1.7205 to 0.4505)
6-8 hours	-0.6471 (-1.6606 to 0.3663)	-0.3088 (-1.3096 to 0.6921)	-0.5332 (-1.5198 to 0.4533)	-0.4713 (-1.5619 to 0.6193)

After Day 1	-0.1568 (-1.1264 to 0.8128)	-0.4151 (-1.3776 to 0.5474)	-0.2348 (-1.1821 to 0.7124)	-0.7065 (-1.7474 to 0.3344)
Day 2	-0.1240 (-1.2034 to 0.9554)	-0.2406 (-1.3149 to 0.8337)	-0.2481 (-1.3142 to 0.8180)	-0.0484 (-1.2105 to 1.1136)
Day 3	-0.4484 (-1.5451 to 0.6483)	-0.5256 (-1.5999 to 0.5487)	-0.0042 (-1.0654 to 1.0569)	-0.4301 (-1.5845 to 0.7243)
Day 4	0.0997 (-0.9847 to 1.1840)	-0.4396 (-1.5139 to 0.6347)	-0.3060 (-1.3722 to 0.7601)	-1.0671 (-2.2363 to 0.1022)
Day 5	-0.1544 (-1.2466 to 0.9379)	-0.4547 (-1.5457 to 0.6364)	-0.3810 (-1.4422 to 0.6802)	-1.2803 (-2.4386 to -0.1220)

Statistical analyses

No statistical analyses for this end point

Secondary: Part C, Change in EEG parameters (relative power of theta frequencies) from baseline

End point title	Part C, Change in EEG parameters (relative power of theta frequencies) from baseline[60]

End point description:

Change from baseline in EEG parameters: Relative power of theta frequencies (average of T3-O1 and T4-O2) (PPASC).

The data are presented by "Dose group" (Per dose group overall, all timepoints), by timepoint (each specific time-point from all 5 days combined), by day (all time-points a specific day combined, "Post-dose" is combined Day 1 data), and by Days 2-5 combined (= After Day 1).
Change from pre-dose at consecutive days has been evaluated (using MMRM). Using the least square mean estimate, no statistically significant difference from placebo was achieved.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 5, 8 hours post dose

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.
In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented.
In Part D of the trial (extended treatment), different measurement timepoints were used and EEG data for Part D are described in separate endpoints.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	Part C, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: percent (%)				
least squares mean (confidence interval 95%)				

Dose group	1.1082 (-3.8616 to 6.0781)	-1.9506 (-6.9313 to 3.0300)	3.4475 (-1.0908 to 7.9858)	-0.1210 (-5.1054 to 4.8634)
Post-dose	0.8595 (-4.1240 to 5.8430)	-1.9939 (-6.9863 to 2.9986)	3.5691 (-0.9795 to 8.1176)	-0.1968 (-5.1957 to 4.8021)
90 min	1.3056 (-3.8162 to 6.4273)	-1.9689 (-7.0928 to 3.1550)	4.2620 (-0.4066 to 8.9306)	0.1682 (-4.9727 to 5.3092)
180 min	1.1782 (-3.9338 to 6.2902)	-1.4291 (-6.5530 to 3.6948)	2.5538 (-2.1077 to 7.2153)	0.4910 (-4.6597 to 5.6417)
6-8 hours	0.0947 (-5.0275 to 5.2169)	-2.5836 (-7.6980 to 2.5307)	3.8914 (-0.7700 to 8.5529)	-1.2496 (-6.4166 to 3.9175)
After Day 1	1.5961 (-3.3911 to 6.5833)	-1.8770 (-6.8735 to 3.1195)	3.5229 (-1.0293 to 8.0751)	0.1009 (-4.9024 to 5.1042)
Day 2	2.3078 (-2.9626 to 7.5782)	-2.1113 (-7.3934 to 3.1708)	3.6616 (-1.1645 to 8.4876)	-1.8738 (-7.2201 to 3.4724)
Day 3	1.3031 (-4.0198 to 6.6261)	-1.7383 (-7.0204 to 3.5438)	3.9723 (-0.8426 to 8.7872)	0.0403 (-5.2816 to 5.3622)
Day 4	1.8476 (-3.4377 to 7.1328)	-2.1406 (-7.4227 to 3.1415)	2.7183 (-2.1077 to 7.5444)	1.3873 (-3.9797 to 6.7542)
Day 5	0.9259 (-4.3809 to 6.2327)	-1.5177 (-6.8516 to 3.8162)	3.7396 (-1.0753 to 8.5544)	0.8499 (-4.4812 to 6.1810)

Statistical analyses

No statistical analyses for this end point

Secondary: Part C, Change in EEG parameters (DTABR) from baseline

End point title	Part C, Change in EEG parameters (DTABR) from baseline[61]

End point description:

Change from baseline in EEG parameters: Ratio relative powers of delta and theta to the relative powers of alpha and beta, DTABR (average of T3-O1 and T4-O2, Part C (PPASC).

The data are presented by "Dose group" (Per dose group overall, all timepoints), by timepoint (each specific time-point from all 5 days combined), by day (all time-points a specific day combined, "Post-dose" is combined Day 1 data), and by Days 2-5 combined (= After Day 1).
Change from pre-dose at consecutive days has been evaluated (using MMRM). Using the least square mean estimate, no statistically significant difference from placebo was achieved.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 5, 8 hours post dose

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.
In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented.
In Part D of the trial (extended treatment), different measurement timepoints were used and EEG data for Part D are described in separate endpoints.

End point values	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)	Part C, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	5	5	5
Units: no unit				
least squares mean (confidence interval 95%)				
Dose group	-0.0257 (-0.4877 to 0.4363)	-0.1113 (-0.5758 to 0.3533)	0.0291 (-0.4315 to 0.4898)	0.0987 (-0.3719 to 0.5692)
Post-dose	-0.0014 (-0.4656 to 0.4627)	-0.0875 (-0.5540 to 0.3790)	0.0626 (-0.3998 to 0.5250)	0.0911 (-0.3819 to 0.5640)
90 min	-0.0486 (-0.5353 to 0.4382)	-0.1595 (-0.6474 to 0.3283)	-0.0156 (-0.4997 to 0.4686)	0.1671 (-0.3286 to 0.6628)
180 min	-0.0900 (-0.5751 to 0.3952)	-0.0741 (-0.5620 to 0.4138)	-0.0495 (-0.5321 to 0.4331)	0.0804 (-0.4170 to 0.5779)
6-8 hours	0.1342 (-0.3527 to 0.6211)	-0.0290 (-0.5153 to 0.4573)	0.2529 (-0.2297 to 0.7355)	0.0256 (-0.4746 to 0.5257)
After Day 1	-0.0429 (-0.5080 to 0.4223)	-0.0962 (-0.5637 to 0.3713)	0.0567 (-0.4068 to 0.5201)	0.1071 (-0.3670 to 0.5811)
Day 2	0.0350 (-0.4824 to 0.5524)	0.0659 (-0.4541 to 0.5859)	0.1652 (-0.3538 to 0.6843)	-0.0696 (-0.6047 to 0.4654)
Day 3	0.1050 (-0.4211 to 0.6310)	-0.1471 (-0.6671 to 0.3729)	-0.0895 (-0.6061 to 0.4271)	0.0110 (-0.5201 to 0.5421)
Day 4	-0.1748 (-0.6946 to 0.3451)	-0.1021 (-0.6221 to 0.4179)	0.0279 (-0.4910 to 0.5469)	0.1463 (-0.3927 to 0.6853)
Day 5	-0.1366 (-0.6601 to 0.3869)	-0.2013 (-0.7295 to 0.3269)	0.1230 (-0.3936 to 0.6396)	0.3406 (-0.1922 to 0.8733)

Statistical analyses

No statistical analyses for this end point

Secondary: Part D, Change in EEG parameters (MDF) from Day 1

End point title	Part D, Change in EEG parameters (MDF) from Day 1[62]

End point description:

Change from Day 1 to Day 21 in the EEG parameter Mean Dominant Frequency, MDF-US (average of T3-O1 and T4-O2)
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.

In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented. In Part C of the trial (5 Days treatment), different measurement timepoints were used and EEG data for Part C are described in separate endpoints.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	9	9	7
Units: Hz				
least squares mean (confidence interval 95%)	0.7544 (-0.6957 to 2.2045)	0.2244 (-0.7313 to 1.1801)	0.3366 (-0.6832 to 1.3564)	-0.5716 (-1.7486 to 0.6054)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: Hz				
least squares mean (confidence interval 95%)	0.4385 (-0.2340 to 1.1109)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, D1 10 mg BID (20 mg per day) v Part D, Total (D1+D2+D3)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1417 [63]
Method	Mixed models analysis
Variability estimate	Standard deviation

Notes:

[63] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.1614
D2 40 mg BID vs placebo: P-value = 0.2953
D3 80 mg BID vs placebo: P-value = 0.2474

Secondary: Part D, Change in EEG parameters (relative power of theta frequencies) from Day 1

End point title	Part D, Change in EEG parameters (relative power of theta frequencies) from Day 1[64]

End point description:

Change from Day 1 to Day 21 in the EEG parameter Relative power of theta frequencies (average of T3-O1 and T4-O2).
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.
In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented.
In Part C of the trial (5 Days treatment), different measurement timepoints were used and EEG data for Part C are described in separate endpoints.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	9	9	7
Units: percent (%)				
least squares mean (confidence interval 95%)	-2.7864 (-12.3875 to 6.8147)	2.4518 (-3.7654 to 8.6690)	2.3061 (-4.0957 to 8.7079)	12.3025 (5.0502 to 19.5548)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: percent (%)				
least squares mean (confidence interval 95%)	0.6572 (-3.6615 to 4.9758)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D1 10 mg BID (20 mg per day) v Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3)
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0086 [65]
Method	Mixed models analysis

Notes:

[65] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.0161
D2 40 mg BID vs placebo: P-value = 0.0436
D3 80 mg BID vs placebo: P-value = 0.0429

Secondary: Part D, Change in EEG parameters (DTABR) from Day 1

End point title	Part D, Change in EEG parameters (DTABR) from Day 1[66]

End point description:

Change from Day 1 to Day 21 in the EEG parameter Ratio relative powers of delta and theta to the relative powers of alpha and beta, DTABR (average of T3-O1 and T4-O2.
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Part A of the trial (healthy volunteers), no efficacy endpoints were evaluated.
In Part B of the trial (single dose), only exploratory measurements of EEG were performed. No comparison with placebo was possible due to lack of evaluable data. No results are therefore presented.
In Part C of the trial (5 Days treatment), different measurement timepoints were used and EEG data for Part C are described in separate endpoints.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	9	9	7
Units: no unit				
least squares mean (confidence interval 95%)	-0.3527 (-0.8891 to 0.1836)	-0.0443 (-0.4043 to 0.3157)	-0.2313 (-0.6133 to 0.1507)	0.3904 (-0.0489 to 0.8296)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: no unit				
least squares mean (confidence interval 95%)	-0.2094 (-0.4586 to 0.0398)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D1 10 mg BID (20 mg per day) v Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3)

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0209 [67]
Method	Mixed models analysis

Notes:

[67] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.0360
D2 40 mg BID vs placebo: P-value = 0.1318
D3 80 mg BID vs placebo: P-value = 0.0360

Secondary: Part D, Change in CRT index from Day 1

End point title	Part D, Change in CRT index from Day 1[68]

End point description:

Change in cognitive function from Day 1 to Day 21, compared to placebo, as measured by the Continuous Reaction Time (CRT) test (PPASD). The CRT method is a computerised registration of a series of motor reaction times to an auditory stimulus.
The CRT test outputs a single number, the CRT-index which is calculated on the basis of the percentiles of the reaction times (50 percentile / (90-10) percentile). This index is a measure of the reaction time and attention stability and can be used to assess deficits in attention and cognition.
A value of the CRT Index of <1.9 discriminates between organic brain damage and HE with a sensitivity and specificity well above 90% and is used as a normal value threshold by the software.

The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A (healthy volunteers) and B (single dose) of the trial, CRT was not evaluated.
In Part C of the trial (5 Days treatment), only Day 1 data were collected and no change was evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: index				
least squares mean (confidence interval 95%)	0.2925 (-0.1222 to 0.7072)	0.3588 (-0.0363 to 0.7540)	0.3425 (-0.0111 to 0.6962)	0.3957 (0.0543 to 0.7372)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: index				
least squares mean (confidence interval 95%)	0.3313 (0.1070 to 0.5556)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3) v Part D, D1 10 mg BID (20 mg per day)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7543 [69]
Method	Mixed models analysis

Notes:

[69] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.7011
D2 40 mg BID vs placebo: P-value = 0.8890
D3 80 mg BID vs placebo: P-value = 0.8295

Secondary: Part D, Change in PHES from Day 1

End point title	Part D, Change in PHES from Day 1[70]

End point description:

Change in cognitive function from Day 1 to Day 21, compared to placebo, as measured by Portosystemic Hepatic Encephalopathy Score (PHES), (PPASD). The PHES is a paper-pencil test, which assesses motor speed, motor accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction and memory, which are related to most of neuropsychological impairments in Covert hepatic encephalopathy (CHE). The sub-tests are scored according to a scoring manual.
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A (healthy volunteers) and B (single dose) of the trial, PHES was not evaluated. In Part C of the trial (5 Days treatment), only Day 1 data were collected and no change was evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
least squares mean (confidence interval 95%)	3.6 (2.0 to 5.1)	1.1 (-0.4 to 2.6)	2.0 (0.7 to 3.3)	1.9 (0.7 to 3.2)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: score				
least squares mean (confidence interval 95%)	2.2 (1.4 to 3.0)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3) v Part D, D1 10 mg BID (20 mg per day)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7019 [71]
Method	Mixed models analysis

Notes:

[71] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.1050
D2 40 mg BID vs placebo: P-value = 0.3979
D3 80 mg BID vs placebo: P-value = 0.9516

Secondary: Part D, Change in ANT1 from Day 1

End point title	Part D, Change in ANT1 from Day 1[72]

End point description:

Change in cognitive function from Day 1 to Day 21, compared to placebo, as measured by the Animal Naming Test (ANT1), (PPASD). The ANT1 is a semantic fluency test that can appraise the cognitive functions impaired in the early stages of HE, mainly executive functions. Study subjects were asked to list as many animals as they could during 1 minute. All repetitions and errors (non-animal words) were excluded from the calculations.
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, ANT1 was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
least squares mean (confidence interval 95%)	4.2 (1.2 to 7.2)	2.2 (-0.5 to 4.9)	2.2 (-0.2 to 4.6)	1.9 (-0.5 to 4.4)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: score				
least squares mean (confidence interval 95%)	2.9 (1.3 to 4.5)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D1 10 mg BID (20 mg per day) v Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5396 [73]
Method	Mixed models analysis

Notes:

[73] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.2616
D2 40 mg BID vs placebo: P-value = 0.8977
D3 80 mg BID vs placebo: P-value = 0.8788

Secondary: Part D, Change in ESS from Day 1

End point title	Part D, Change in ESS from Day 1[74]

End point description:

Change in daytime sleepiness from Day 1 to Day 21, compared to placebo, as measured by the Epworth Sleepiness Scale (ESS), (PPASD). The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The ESS score (the sum of 8 item scores, 0-3) can range from 0 to 24. The higher the ESS score, the higher that person’s average sleep propensity in daily life, or their ‘daytime sleepiness’.
The change from Day 1 to Day 21 is presented by Dose group and in Total (all dose groups D1-D3 combined).

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, EES was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
least squares mean (confidence interval 95%)	-0.7 (-2.4 to 0.9)	-3.0 (-4.6 to -1.3)	-1.4 (-2.8 to 0.0)	-0.0 (-1.4 to 1.3)

End point values	Part D, Total (D1+D2+D3)			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: score				
least squares mean (confidence interval 95%)	-1.7 (-2.6 to -0.8)			

Statistical analyses

Statistical analysis title	MMRM

Statistical analysis description:

A Mixed Model Repeated Measures (MMRM) analysis was used to estimate the statistics presented.

Comparison groups	Part D, D1 10 mg BID (20 mg per day) v Part D, D2 40 mg BID (80 mg per day) v Part D, D3 80 mg BID (160 mg per day) v Part D, Placebo v Part D, Total (D1+D2+D3)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0448 [75]
Method	Mixed models analysis

Notes:

[75] - = Group Total (D1+D2+D3) vs placebo
D1 10 mg BID vs placebo: P-value = 0.5263
D2 40 mg BID vs placebo: P-value = 0.0075
D3 80 mg BID vs placebo: P-value = 0.1703

Secondary: Part D, Change in caregiver QoL (time dependency) from Day 1

End point title	Part D, Change in caregiver QoL (time dependency) from Day

End point description:

Change in caregiver quality of life (QoL) from Day 1 to Day 21, as measured by the CGBI questionnaire (PPASD). The CGBI is a standardised questionnaire consisting of 24 questions grouped into 5 dimensions (time dependency, development, physical health, emotional health, social relationships). There are 5 items in each dimension, except for physical burden which has 4 items. A higher score indicates a greater caregiver burden.
The change in time dependency from Day 1 to Day 21 is presented by Dose group.

No general trend of dose dependent better improvement in the GR3027 dose groups as compared to placebo was seen for time dependency.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, caregiver QoL was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
arithmetic mean (standard deviation)	-0.1 (± 0.4)	0.0 (± 0.5)	-0.5 (± 1.2)	-0.5 (± 1.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Part D, Change in caregiver QoL (development) from Day 1

End point title	Part D, Change in caregiver QoL (development) from Day 1[77]

End point description:

Change in caregiver quality of life (QoL) from Day 1 to Day 21, as measured by the CGBI questionnaire (PPASD). The CGBI is a standardised questionnaire consisting of 24 questions grouped into 5 dimensions (time dependency, development, physical health, emotional health, social relationships). There are 5 items in each dimension, except for physical burden which has 4 items. A higher score indicates a greater caregiver burden.
The change in development from Day 1 to Day 21 is presented by Dose group.

No general trend of dose dependent better improvement in the GR3027 dose groups as compared to placebo was seen for development .

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, caregiver QoL was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
arithmetic mean (standard deviation)	-0.4 (± 1.1)	0.0 (± 0.0)	0.0 (± 0.4)	0.1 (± 1.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Part D, Change in caregiver QoL (physical health) from Day 1

End point title	Part D, Change in caregiver QoL (physical health) from Day

End point description:

Change in caregiver quality of life (QoL) from Day 1 to Day 21, as measured by the CGBI questionnaire (PPASD). The CGBI is a standardised questionnaire consisting of 24 questions grouped into 5 dimensions (time dependency, development, physical health, emotional health, social relationships). There are 5 items in each dimension, except for physical burden which has 4 items. A higher score indicates a greater caregiver burden.
The change in time physical health from Day 1 to Day 21 is presented by Dose group.

No general trend of dose dependent better improvement in the GR3027 dose groups as compared to placebo was seen for physical health.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[78] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, caregiver QoL was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
arithmetic mean (standard deviation)	-0.6 (± 1.4)	0.2 (± 0.7)	-0.1 (± 0.7)	-0.3 (± 0.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Part D, Change in caregiver QoL (emotional health) from Day 1

End point title	Part D, Change in caregiver QoL (emotional health) from Day

End point description:

Change in caregiver quality of life (QoL) from Day 1 to Day 21, as measured by the CGBI questionnaire (PPASD). The CGBI is a standardised questionnaire consisting of 24 questions grouped into 5 dimensions (time dependency, development, physical health, emotional health, social relationships). There are 5 items in each dimension, except for physical burden which has 4 items. A higher score indicates a greater caregiver burden.
The change in emotional health from Day 1 to Day 21 is presented by Dose group.

No general trend of dose dependent better improvement in the GR3027 dose groups as compared to placebo was seen for emotional health.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, caregiver QoL was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
arithmetic mean (standard deviation)	-0.3 (± 0.5)	0.4 (± 1.7)	-0.2 (± 0.4)	0.0 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Part D, Change in caregiver QoL (social relationships) from Day 1

End point title	Part D, Change in caregiver QoL (social relationships) from Day 1[80]

End point description:

Change in caregiver quality of life (QoL) from Day 1 to Day 21, as measured by the CGBI questionnaire (PPASD). The CGBI is a standardised questionnaire consisting of 24 questions grouped into 5 dimensions (time dependency, development, physical health, emotional health, social relationships). There are 5 items in each dimension, except for physical burden which has 4 items. A higher score indicates a greater caregiver burden.
The change in social relationships from Day 1 to Day 21 is presented by Dose group.

No general trend of dose dependent better improvement in the GR3027 dose groups as compared to placebo was seen for social relationships.

End point type	Secondary

End point timeframe:

Predose Day 1 to Day 21

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: In Parts A, B, and C of the trial, caregiver QoL was not evaluated.

End point values	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	9	11	12
Units: score				
arithmetic mean (standard deviation)	-0.3 (± 0.5)	0.0 (± 0.0)	-0.2 (± 1.0)	0.0 (± 0.9)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were collected from the first administration of the IMP, Day 1, and until 21 days past the last dose in all trial parts.

Adverse event reporting additional description:

TEAEs, physical examination, laboratory values, vital signs, and ECG parameters reported during the study were summarized for all subjects. Abnormal, clinically significant findings during physical examinations and ECG assessments were to be reported as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Part A, A1 50 mg QD

Reporting group description:

Healthy male subjects recieved an oral dose of 50 mg GR3027 QD for 5 days.

Reporting group title	Part A, A2 50 mg BID (100 mg per day)

Reporting group description:

Healthy male subjects recieved oral doses of 50 mg GR3027 BID for 5 days.

Reporting group title	Part A, A3 100 mg BID (200 mg per day)

Reporting group description:

Healthy male subjects recieved oral doses of 100 mg GR3027 BID for 5 days.

Reporting group title	Part A, Placebo

Reporting group description:

Healthy male subjects recieved placebo capsules QD (cohort A1) or BID (cohorts A2-A3) for 5 days.

Reporting group title	Part B, 10 mg SD

Reporting group description:

Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of 10 mg GR3027

Reporting group title	Part B, Placebo

Reporting group description:

Cirrhotic patients, Child-Pugh class B, recieved a single oral dose of placebo

Reporting group title	Part C, C1 10 mg BID (20 mg per day)

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 5 days

Reporting group title	Part C, C2 40 mg BID (80 mg per day)

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 5 days

Reporting group title	Part C, C3 80 mg BID (160 mg per day)

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 5 days

Reporting group title	Part C, Placebo

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 5 days.

Reporting group title	Part D, D1 10 mg BID (20 mg per day)

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 10 mg GR3027 BID for 21 days

Reporting group title	Part D, D2 40 mg BID (80 mg per day)

Reporting group description:

Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 40 mg GR3027 BID for 21 days

Reporting group title	Part D, D3 80 mg BID (160 mg per day)
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved oral doses of 80 mg GR3027 BID for 21 days	
Reporting group title	Part D, Placebo
Reporting group description:	
Cirrhotic patients, Child-Pugh class A and B, recieved placebo capsules BID for 21 days.	

Serious adverse events	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Toxic encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part A, Placebo	Part B, 10 mg SD	Part B, Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Toxic encephalopathy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Toxic encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part C, Placebo	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)
Total subjects affected by serious			

adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Toxic encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Toxic encephalopathy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A, A1 50 mg QD	Part A, A2 50 mg BID (100 mg per day)	Part A, A3 100 mg BID (200 mg per day)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 6 (33.33%)	4 / 6 (66.67%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vertigo CNS origin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	4
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Flatulence			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Nausea			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part A, Placebo	Part B, 10 mg SD	Part B, Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	1 / 2 (50.00%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Fatigue			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vertigo CNS origin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part C, C1 10 mg BID (20 mg per day)	Part C, C2 40 mg BID (80 mg per day)	Part C, C3 80 mg BID (160 mg per day)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	1 / 6 (16.67%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Thirst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vertigo CNS origin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part C, Placebo	Part D, D1 10 mg BID (20 mg per day)	Part D, D2 40 mg BID (80 mg per day)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	2 / 10 (20.00%)	3 / 10 (30.00%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Thirst			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bilirubin conjugated increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ventricular tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	9
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vertigo CNS origin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			

subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 10 (10.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 10 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part D, D3 80 mg BID (160 mg per day)	Part D, Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	4 / 12 (33.33%)	
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Thirst			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

Bilirubin conjugated increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
International normalised ratio increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Metabolic cardiomyopathy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Ventricular tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Somnolence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

Syncope			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Vertigo CNS origin			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
occurrences (all)	2	2	
Dyspepsia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue			

disorders Back pain subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1	 0 / 12 (0.00%) 0	
Infections and infestations Sinusitis subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0	 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0	 1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2017	Revised upper age limit for cirrhotic patients: The upper age limit was revised from 65 to 70 years.
22 November 2017	1 Starting dose in Part C Based on safety and PK data from trial Parts A and B, the dose of GR3027 to be administered in the first dose group in part C was 10 mg BID. 2 Exclusion of Quality of Life assessment in Part D It was decided to exclude the Sickness Impact Profile (SIP) questionnaire for preliminary effect on Quality of Life from the trial as it was not validated for use in Ukraine. 3 Additional efficacy assessment in Part D Assessment of Animal Naming Test (ANT1) was added to the battery of tests for the evaluation of preliminary efficacy in the trial as it was expected to increase the opportunity to evaluate cognitive function in patients with HE. 4 Inclusion of women of non-childbearing potential Inclusion of women of non-childbearing potential in Parts C and D of the trial was proposed based on non-clinical data and the safety profile of GR3027 as seen in Parts A and B of the trial. 5 Deletion of exclusion criterion reg. transplantation list (cirrhotic patients) Exclusion criterion No. 10 (Expected to undergo transplantation within 6 months after randomization) was deleted as it was considered to be covered by the exclusion criterion Any planned major surgery within the duration of the trial. 6 No urine PK in Part C As very low concentrations of GR3027 were detected in urine in healthy subjects (Part A) in this trial, a low degree of renal elimination was indicated. Therefore, urine was not to be collected for PK analysis in Part C. 7 Re-screening procedure A procedure for re-screening was defined to allow for re-assessment/re-screening, to a limited extent, of subjects based on parameters expected to fluctuate over time in the target patient population. 8 Portable EEG device to be used in Part C To facilitate the procedures at the sites and to minimize the burden on the subjects in terms of efficacy assessments, it was decided that the portable EEG device intended for trial Part D was to be used already in Part C.
31 January 2018	Change of PI at the CTC Clinic in Linköping, Sweden. (Site was not initiated.)
22 March 2018	The upper BMI limit for inclusion of subjects with liver cirrhosis in parts C and D was increased from 35 to 40 kg/m2 to allow more complete representation of obese subjects while excluding those with morbid obesity. This modification was intended to enhance the scientific value of the study with respect to the population at risk for covert HE without compromising subject safety. The upper weight limit was also excluded.

24 October 2018	1 Inclusion of Child-Pugh A patients in trial Part C Enrolment of up to 50% Child-Pugh A patients into each dose group of Part C was introduced. This allowed evaluation of safety and PK in a trial population more representative of the target population of cirrhotic patients with CHE. 2 Revision of inclusion criterion No. 8 (inclusion based on manifestations of CHE) The ANT1 was included as a test for screening subjects for the presence of CHE. 3 Revision of exclusion criterion no. 2 (GI bleeding) The required period with no active GI bleeding or a history of GI bleeding requiring blood transfusion prior to randomization was shortened from 12 to 3 months. 4 Revision of exclusion criterion no. 13 (vital signs ranges at screening) The exclusion criterion was modified to reflect the range observed by continuous 24 h recording in an unselected population of clinically stable subjects with cirrhosis. The lower limit of systolic blood pressure was set to <90 mm Hg, the lower limit of diastolic blood pressure was set to <50 mm Hg, and the limit of heart rate were set to <50 or >110 beats per minute. 5 Sample size modification in Part D At the discretion of the Sponsor, the sample size of 1 or more cohorts in Part D could be increased from 14 up to 21 (placebo/GR3027; 1:2.5) to maximize the likelihood of achieving the Part D objectives, in particular to increase the statistical likelihood of distinguishing among doses and identifying the optimal efficacy measure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported