Clinical trial results:
Bioavailability and Food Effect of Experimental Glecaprevir + Pibrentasvir Pediatric Formulation in Healthy Adult Subjects

Summary

EudraCT number	2019-003736-22
Trial protocol	Outside EU/EEA
Global end of trial date	05 April 2018

Results information

Result version number	v1 (current)
This version publication date	03 December 2020
First version publication date	03 December 2020

Trial information

Trial identification

Sponsor protocol code	M17-142

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001832-PIP01-15
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	05 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the bioavailability of the experimental glecaprevir (GLE) + pibrentasvir (PIB) pediatric formulation relative to the reference Phase 3 adult formulation under fasting and non-fasting conditions.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 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	United States: 39
Worldwide total number of subjects	39
EEA total number of subjects	0

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)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label, randomized, crossover study conducted in 2 parts that enrolled healthy males and females between 18 and 55 years of age, inclusive.

Pre-assignment

Screening details:

Part 1: 4-sequence, 4-period crossover design to evaluate bioavailability of GLE+PIB pediatric formulation relative to commercial adult formulation under fasting/non-fasting conditions. Part 2: 3-sequence, 3-period crossover design to evaluate effect of high-fat and low-fat meals on GLE+PIB pediatric formulation relative to fasting conditions.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Regimen Sequence ABCD

Arm description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Investigational medicinal product name	glecaprevir (GLE)/pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Adult formulation, GLE 100 mg / PIB 40 mg per tablet

Arm title	Part 1: Regimen Sequence BDAC

Arm description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Investigational medicinal product name	glecaprevir (GLE)/pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Adult formulation, GLC 100 mg / BIB 40 mg per tablet

Arm title	Part 1: Regimen Sequence CADB

Arm description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Investigational medicinal product name	glecaprevir (GLE)/pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Adult formulation, GLE 100 mg / PIB 40 mg per tablet

Arm title	Part 1: Regimen Sequence DCBA

Arm description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Investigational medicinal product name	glecaprevir (GLE)/pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Adult formulation, GLE 100 mg / PIB 40 mg per tablet

Arm title	Part 2: Regimen Sequence EFG

Arm description:

In Part 2, subjects received 3 doses of GLE+PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Arm title	Part 2: Regimen Sequence FGE

Arm description:

In Part 2, subjects received 3 doses of GLE +PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Arm title	Part 2: Regimen Sequence GEF

Arm description:

In Part 2, subjects received 3 doses of GLE + PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.

Arm type	Experimental
Investigational medicinal product name	glecaprevir (GLE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation,15.67% (w/w) strength

Investigational medicinal product name	pibrentasvir (PIB)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Film-coated pellets, pediatric formulation, 8.25% (w/w) strength

Number of subjects in period 1	Part 1: Regimen Sequence ABCD	Part 1: Regimen Sequence BDAC	Part 1: Regimen Sequence CADB
Started	6	6	6
Completed	6	6	5
Not completed	0	0	1
Adverse event	-	-	1

Number of subjects in period 1	Part 1: Regimen Sequence DCBA	Part 2: Regimen Sequence EFG	Part 2: Regimen Sequence FGE
Started	6	5	5
Completed	6	5	5
Not completed	0	0	0
Adverse event	-	-	-

Number of subjects in period 1	Part 2: Regimen Sequence GEF
Started	5
Completed	5
Not completed	0
Adverse event	-

Baseline characteristics

Reporting groups

Reporting group title	Part 1: Regimen Sequence ABCD

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.

Reporting group title	Part 1: Regimen Sequence BDAC

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.

Reporting group title	Part 1: Regimen Sequence CADB

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.

Reporting group title	Part 1: Regimen Sequence DCBA

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.

Reporting group title	Part 2: Regimen Sequence EFG

Reporting group description:

In Part 2, subjects received 3 doses of GLE+PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.

Reporting group title	Part 2: Regimen Sequence FGE

Reporting group description:

In Part 2, subjects received 3 doses of GLE +PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.

Reporting group title	Part 2: Regimen Sequence GEF

Reporting group description:

In Part 2, subjects received 3 doses of GLE + PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.

Reporting group values	Part 1: Regimen Sequence ABCD	Part 1: Regimen Sequence BDAC	Part 1: Regimen Sequence CADB
Number of subjects	6	6	6
Age categorical Units: Subjects			
Adults (18-64 years)	6	6	6
Age continuous Units: years			
arithmetic mean	44.5	34.0	44.2
standard deviation	± 6.16	± 7.51	± 7.31
Gender categorical Units: Subjects			
Female	3	3	4
Male	3	3	2
Race Units: Subjects			
White	4	3	3
Black or African American	2	3	3
Multi-race	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	0
None of the above	5	5	6

Reporting group values	Part 1: Regimen Sequence DCBA	Part 2: Regimen Sequence EFG	Part 2: Regimen Sequence FGE
Number of subjects	6	5	5
Age categorical Units: Subjects			
Adults (18-64 years)	6	5	5
Age continuous Units: years			
arithmetic mean	40.2	39.4	32.4
standard deviation	± 10.53	± 10.21	± 4.16
Gender categorical Units: Subjects			
Female	3	1	0
Male	3	4	5
Race Units: Subjects			
White	4	3	4
Black or African American	2	1	0
Multi-race	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
None of the above	6	4	4

Reporting group values	Part 2: Regimen Sequence GEF	Total	

Number of subjects	5	39	
Age categorical Units: Subjects			
Adults (18-64 years)	5	39	
Age continuous Units: years			
arithmetic mean	32.6		
standard deviation	± 9.71	-	
Gender categorical Units: Subjects			
Female	0	14	
Male	5	25	
Race Units: Subjects			
White	4	25	
Black or African American	0	11	
Multi-race	1	3	
Ethnicity Units: Subjects			
Hispanic or Latino	2	6	
None of the above	3	33	

End points

End points reporting groups

Reporting group title	Part 1: Regimen Sequence ABCD

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.

Reporting group title	Part 1: Regimen Sequence BDAC

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.

Reporting group title	Part 1: Regimen Sequence CADB

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.

Reporting group title	Part 1: Regimen Sequence DCBA

Reporting group description:

In Part 1, subjects received 2 doses of GLE + PIB pediatric formulations and 2 doses of GLE/PIB adult formulation with a washout interval of at least 4 days between doses:
Regimen D: single dose of GLE/PIB 300 mg/120 mg tablets administered under non-fasting conditions.
Regimen C: single dose of GLE/PIB 300 mg/120 mg tablets administered under fasting conditions.
Regimen B: single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.
Regimen A: single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.

Reporting group title	Part 2: Regimen Sequence EFG

Reporting group description:

In Part 2, subjects received 3 doses of GLE+PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.

Reporting group title	Part 2: Regimen Sequence FGE

Reporting group description:

In Part 2, subjects received 3 doses of GLE +PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.

Reporting group title	Part 2: Regimen Sequence GEF

Reporting group description:

In Part 2, subjects received 3 doses of GLE + PIB pediatric formulations with a washout interval of 5 days between doses:
Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.
Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.
Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.

Subject analysis set title	Regimen A
Subject analysis set type	Full analysis

Subject analysis set description:

Single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.

Subject analysis set title	Regimen B
Subject analysis set type	Full analysis

Subject analysis set description:

Single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.

Subject analysis set title	Regimen C
Subject analysis set type	Full analysis

Subject analysis set description:

Single dose of GLE /PIB 300/120 mg tablets administered under fasting conditions.

Subject analysis set title	Regimen D
Subject analysis set type	Full analysis

Subject analysis set description:

Single dose of GLE /PIB 300/120 mg tablets administered under non-fasting conditions.

Subject analysis set title	Regimen E
Subject analysis set type	Full analysis

Subject analysis set description:

Regimen E: Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.

Subject analysis set title	Regimen F
Subject analysis set type	Full analysis

Subject analysis set description:

Regimen F: Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.

Subject analysis set title	Regimen G
Subject analysis set type	Full analysis

Subject analysis set description:

Regimen G: Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.

Primary: Number of Subjects Treatment-Emergent Adverse Events

End point title	Number of Subjects Treatment-Emergent Adverse Events[1]

End point description:

An AE is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with treatment. A serious AE is an event that: results in death; is life-threatening; results in hospitalization or prolongation of hospitalization; is a congentical anomaly; results in significant disability/incapacity; is an important medical event.

End point type	Primary

End point timeframe:

Part 1: From first dose of study treatment through the end of the last treatment (up to 19 days) plus 30 days. Part 2: From first dose of study treatment through the end of the last treatment (up to 11 days) plus 30 days.

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: Descriptive statistics are presented per protocol.

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: subjects				
Any adverse event (AE)	2	1	2	1
Any AE possibly related to regimen A	0	0	0	0

Any AE possibly related to regimen B	0	0	0	0
Any AE possibly related to regimen C	0	0	0	0
Any AE possibly related to regimen D	0	0	0	0
Any serious AE	0	0	0	0
Any AE leading to discontinuation of study drug	1	0	0	0
Any fatal AE	0	0	0	0
Deaths	0	0	0	0

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: subjects				
Any adverse event (AE)	0	0	0	
Any AE possibly related to regimen A	0	0	0	
Any AE possibly related to regimen B	0	0	0	
Any AE possibly related to regimen C	0	0	0	
Any AE possibly related to regimen D	0	0	0	
Any serious AE	0	0	0	
Any AE leading to discontinuation of study drug	0	0	0	
Any fatal AE	0	0	0	
Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 GLE Pharmacokinetics: Maximum Observed Plasma Concentration (Cmax)

End point title	Part 1 GLE Pharmacokinetics: Maximum Observed Plasma Concentration (Cmax)

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng/mL				
geometric mean (geometric coefficient of variation)	236 (± 144)	621 (± 51)	399 (± 97)	946 (± 83)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Subjects in this analysis: 24 (not 48, per below) Comparison groups: Regimen A vs. Regimen C (not Regimen C vs. Regimen A, per below)	
Comparison groups	Regimen C v Regimen A
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Relative bioavailability
Point estimate	0.591
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.447
upper limit	0.782

Notes:

[2] - Bioequivalence

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Subjects in this analysis: 23 (not 46, per below)	
Comparison groups	Regimen B v Regimen D
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Relative bioavailability
Point estimate	0.664
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.524
upper limit	0.842

Notes:

[3] - Bioequivalence

Primary: Part 1 GLE Pharmacokinetics: Time to Maximum Observed Plasma Concentration (Tmax)

End point title	Part 1 GLE Pharmacokinetics: Time to Maximum Observed Plasma Concentration (Tmax)[4]
End point description:	
End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[4] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: hours				
median (full range (min-max))	1.5 (1.0 to 6.0)	3.0 (1.5 to 6.0)	3.0 (2.0 to 6.0)	4.0 (2.0 to 6.0)

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 GLE Pharmacokinetics: Terminal Phase Elimination Half-Life (t1/2)

End point title	Part 1 GLE Pharmacokinetics: Terminal Phase Elimination Half-Life (t1/2)[5]

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[5] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: hours				
median (full range (min-max))	7.78 (2.85 to 9.51)	7.10 (4.77 to 10.3)	7.11 (4.23 to 9.50)	6.67 (4.00 to 9.69)

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 GLE Pharmacokinetics: Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Measurable Concentration (AUCt)

End point title	Part 1 GLE Pharmacokinetics: Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Measurable Concentration (AUCt)

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1110 (± 118)	2700 (± 50)	1830 (± 78)	3410 (± 76)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 24 (not 48, per below)

Comparison groups	Regimen A v Regimen C
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[6]
Parameter estimate	Relative bioavailability
Point estimate	0.606
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.478
upper limit	0.768

Notes:

[6] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Subjects in this analysis: 23 (not 46, per below)

Comparison groups	Regimen B v Regimen D
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[7]
Parameter estimate	Relative bioavailability
Point estimate	0.794
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.664
upper limit	0.949

Notes:
[7] - Bioequivalence

Primary: Part 1 GLE Pharmacokinetics: Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUCinf)

End point title	Part 1 GLE Pharmacokinetics: Area Under the Plasma Concentration-Time Curve From Time 0 to Infinite Time (AUCinf)

End point description:

End point type	Primary

End point timeframe:
Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1110 (± 118)	2710 (± 50)	1830 (± 78)	3420 (± 76)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:
Subjects in this analysis: 24 (not 48, per below)

Comparison groups	Regimen A v Regimen C
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[8]
Parameter estimate	Relative bioavailability
Point estimate	0.607
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.479
upper limit	0.769

Notes:
[8] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
Subjects in this analysis: 23 (not 46, per below)

Comparison groups	Regimen B v Regimen D

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Parameter estimate	Relative bioavailability
Point estimate	0.795
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.665
upper limit	0.95

Notes:

[9] - Bioequivalence

Primary: Part 1 PIB Pharmacokinetics: Cmax

End point title	Part 1 PIB Pharmacokinetics: Cmax

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng/mL				
geometric mean (geometric coefficient of variation)	102 (± 61)	213 (± 51)	124 (± 63)	189 (± 58)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 24 (not 48, per below)

Comparison groups	Regimen A v Regimen C
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[10]
Parameter estimate	Relative bioavailability
Point estimate	0.822
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.659
upper limit	1.025

Notes:
[10] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
Subjects in this analysis: 23 (not 46, per below)

Comparison groups	Regimen B v Regimen D
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Relative bioavailability
Point estimate	1.137
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.908
upper limit	1.424

Notes:
[11] - Bioequivalence

Primary: Part 1 PIB Pharmacokinetics: Tmax

End point title	Part 1 PIB Pharmacokinetics: Tmax[12]

End point description:

End point type	Primary

End point timeframe:
Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:
[12] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: hours				
median (full range (min-max))	4.0 (3.0 to 5.0)	5.0 (3.0 to 6.0)	5.0 (2.0 to 6.0)	5.0 (2.0 to 8.0)

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 PIB Pharmacokinetics: t1/2

End point title	Part 1 PIB Pharmacokinetics: t1/2[13]

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[13] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: hours				
median (full range (min-max))	14.4 (11.5 to 23.2)	14.1 (11.5 to 16.1)	14.3 (10.5 to 17.6)	14.0 (11.6 to 17.5)

Statistical analyses

No statistical analyses for this end point

Primary: Part 1 PIB Pharmacokinetics: AUCt

End point title	Part 1 PIB Pharmacokinetics: AUCt

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	869 (± 65)	1490 (± 52)	1010 (± 67)	1240 (± 60)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 24 (not 48, per below)

Comparison groups	Regimen A v Regimen C

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[14]
Parameter estimate	Relative bioavailability
Point estimate	0.859
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	1.07

Notes:

[14] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Subjects in this analysis: 23 (not 46, per below)

Comparison groups	Regimen B v Regimen D
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[15]
Parameter estimate	Relative bioavailability
Point estimate	1.223
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.977
upper limit	1.531

Notes:

[15] - Bioequivalence

Primary: Part 1 PIB Pharmacokinetics: AUCinf

End point title	Part 1 PIB Pharmacokinetics: AUCinf

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen A	Regimen B	Regimen C	Regimen D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	23	24	23
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	924 (± 64)	1580 (± 52)	1070 (± 68)	1310 (± 59)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Subjects in this analysis: 24 (not 48, per below)	
Comparison groups	Regimen A v Regimen C
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence[16]
Parameter estimate	Relative bioavailability
Point estimate	0.862
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.695
upper limit	1.07

Notes:
[16] - Bioequivalence

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Subjects in this analysis: 23 (not 46, per below)	
Comparison groups	Regimen B v Regimen D
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[17]
Parameter estimate	Relative bioavailability
Point estimate	1.219
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.978
upper limit	1.52

Notes:
[17] - Bioequivalence

Primary: Part 2 GLE Pharmacokinetics: Cmax

End point title	Part 2 GLE Pharmacokinetics: Cmax
End point description:	

End point type	Primary
End point timeframe:	
Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose	

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	284 (± 64)	387 (± 50)	134 (± 40)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 15 (not 30, per below)

Comparison groups	Regimen E v Regimen G
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[18]
Parameter estimate	Relative bioavailability
Point estimate	2.119
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.732
upper limit	2.592

Notes:

[18] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Subjects in this analysis: 15 (not 30, per below)
Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)

Comparison groups	Regimen G v Regimen F
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[19]
Parameter estimate	Relative bioavailability
Point estimate	2.888
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.361
upper limit	3.533

Notes:

[19] - Bioequivalence

Primary: Part 2 GLE Pharmacokinetics: Tmax

End point title	Part 2 GLE Pharmacokinetics: Tmax[20]

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[20] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: hours				
median (full range (min-max))	4.0 (1.5 to 6.0)	3.0 (1.0 to 6.0)	1.5 (1.0 to 2.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 2 GLE Pharmacokinetics: t1/2

End point title	Part 2 GLE Pharmacokinetics: t1/2[21]

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[21] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: hours				
median (full range (min-max))	6.02 (2.95 to 8.76)	5.85 (5.15 to 10.5)	5.83 (3.04 to 8.35)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 2 GLE Pharmacokinetics: AUCt

End point title	Part 2 GLE Pharmacokinetics: AUCt

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1350 (± 48)	1560 (± 46)	585 (± 48)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Subjects in this analysis: 15 (not 30, per the below)	
Comparison groups	Regimen E v Regimen G
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[22]
Parameter estimate	Relative bioavailability
Point estimate	2.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.985
upper limit	2.688

Notes:

[22] - Bioequivalence

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Subjects in this analysis: 15 (not 30, per the below) Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)	
Comparison groups	Regimen G v Regimen F
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[23]
Parameter estimate	Relative bioavailability
Point estimate	2.676
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.299
upper limit	3.114

Notes:
[23] - Bioequivalence

Primary: Part 2 GLE Pharmacokinetics: AUCinf

End point title	Part 2 GLE Pharmacokinetics: AUCinf

End point description:

End point type	Primary

End point timeframe:
Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1360 (± 48)	1570 (± 46)	589 (± 48)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:
Subjects in this analysis: 15 (not 30, per below)

Comparison groups	Regimen E v Regimen G
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[24]
Parameter estimate	Relative bioavailability
Point estimate	2.305
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.981
upper limit	2.681

Notes:
[24] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
Subjects in this analysis: 15 (not 30, per the below)
Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)

Comparison groups	Regimen G v Regimen F

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[25]
Parameter estimate	Relative bioavailability
Point estimate	2.666
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.292
upper limit	3.101

Notes:

[25] - Bioequivalence

Primary: Part 2 PIB Pharmacokinetics: Cmax

End point title	Part 2 PIB Pharmacokinetics: Cmax

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	189 (± 54)	151 (± 58)	82.2 (± 46)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 15 (not 30, per the below)

Comparison groups	Regimen E v Regimen G
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[26]
Parameter estimate	Relative bioavailability
Point estimate	2.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.867
upper limit	2.834

Notes:
[26] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:
Subjects in this analysis: 15 (not 30, per the below)
Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)

Comparison groups	Regimen G v Regimen F
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[27]
Parameter estimate	Relative bioavailability
Point estimate	1.834
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.489
upper limit	2.26

Notes:
[27] - Bioequivalence

Primary: Part 2 PIB Pharmacokinetics: Tmax

End point title	Part 2 PIB Pharmacokinetics: Tmax[28]

End point description:

End point type	Primary

End point timeframe:
Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:
[28] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: hours				
median (full range (min-max))	5.0 (2.0 to 6.0)	3.0 (2.0 to 5.0)	4.0 (2.0 to 5.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 2 PIB Pharmacokinetics: t1/2

End point title	Part 2 PIB Pharmacokinetics: t1/2[29]

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

Notes:

[29] - 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: Statistical analyses of pharmacokinetic parameters are presented in the data table per protocol.

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: hours				
median (full range (min-max))	12.5 (11.2 to 15.9)	13.1 (10.6 to 15.7)	13.0 (11.8 to 17.2)	

Statistical analyses

No statistical analyses for this end point

Primary: Part 2 PIB Pharmacokinetics: AUCt

End point title	Part 2 PIB Pharmacokinetics: AUCt

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1400 (± 52)	1020 (± 63)	653 (± 49)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Subjects in this analysis: 15 (not 30, per the below)

Comparison groups	Regimen E v Regimen G

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[30]
Parameter estimate	Relative bioavailability
Point estimate	2.145
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.75
upper limit	2.629

Notes:

[30] - Bioequivalence

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Subjects in this analysis: 15 (not 30, per below)
Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)

Comparison groups	Regimen G v Regimen F
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[31]
Parameter estimate	Relative bioavailability
Point estimate	1.566
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.277
upper limit	1.919

Notes:

[31] - Bioequivalence

Primary: Part 2 PIB Pharmacokinetics: AUCinf

End point title	Part 2 PIB Pharmacokinetics: AUCinf

End point description:

End point type	Primary

End point timeframe:

Pre-dose, 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 hours post-dose

End point values	Regimen E	Regimen F	Regimen G	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	15	15	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1470 (± 52)	1070 (± 63)	686 (± 49)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Subjects in this analysis: 15 (not 30, per below)	
Comparison groups	Regimen E v Regimen G
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[32]
Parameter estimate	Relative bioavailability
Point estimate	2.138
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.75
upper limit	2.613

Notes:

[32] - Bioequivalence

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Subjects in this analysis: 15 (not 30, per below) Comparison groups: Regimen F vs. Regimen G (not Regimen G vs. Regimen F, per below)	
Comparison groups	Regimen G v Regimen F
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	equivalence[33]
Parameter estimate	Relative bioavailability
Point estimate	1.562
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.278
upper limit	1.908

Notes:

[33] - Bioequivalence

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: From first dose of study treatment through the end of the last treatment (up to 19 days) plus 30 days. Part 2: From first dose of study treatment through the end of the last treatment (up to 11 days) plus 30 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Regimen A

Reporting group description:

Single dose of GLE 300 mg and PIB 120 mg pellets administered under fasting conditions.

Reporting group title	Regimen B

Reporting group description:

Single dose of GLE 300 mg and PIB 120 mg pellets administered under non-fasting conditions.

Reporting group title	Regimen C

Reporting group description:

Single dose of GLE /PIB 300/120 mg tablets administered under fasting conditions.

Reporting group title	Regimen D

Reporting group description:

Single dose of GLE /PIB 300/120 mg tablets administered under non-fasting conditions.

Reporting group title	Regimen E

Reporting group description:

Single dose of GLE 300 mg and PIB 120 mg administered under high-fat conditions.

Reporting group title	Regimen F

Reporting group description:

Single dose of GLE 300 mg and PIB 120 mg administered under low-fat conditions.

Reporting group title	Regimen G

Reporting group description:

Single dose of GLE 300 mg and PIB 120 mg administered under fasting conditions.

Serious adverse events	Regimen A	Regimen B	Regimen C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Regimen D	Regimen E	Regimen F
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events			

Serious adverse events	Regimen G		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Regimen A	Regimen B	Regimen C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	1 / 23 (4.35%)	2 / 24 (8.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 23 (4.35%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Infectious mononucleosis			

subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 23 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Regimen D	Regimen E	Regimen F
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	0 / 15 (0.00%)	0 / 15 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infectious mononucleosis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 15 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Regimen G		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	0 / 15 (0.00%)		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Infections and infestations Infectious mononucleosis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2017	The purpose of this amendment is to incorporate changes summarized below: - Modify the study design for Part 2. Rationale: To add evaluation of the effect of low-fat meal on the experimental GLE + PIB pediatric formulation to Part 2. Evaluation of different meal types in addition to the standard meal studied in Part 1 will generate data on various types of dietary habits with the pediatric pellet formulation.
14 February 2018	Section 3.13, Meals Updated to specify low-fat meal content for Part 2 for the added regimen. Section 3.14, Confinement Updated confinement details for Part 2 to account for the updated study design. Section 3.15, Follow-Up Updated follow-up details for Part 2 to account for the updated study design. Section 5.1, Treatments Administered Added low-fat regimen in Part 2. Section 5.3, Method of Assigning Subjects to Treatment Groups Updated description for Part 2 to match updated study design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported