



Clinical trial results:

A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Pilot and Dose-Ranging Study of GDC-0853 in Patients with Refractory Chronic Spontaneous Urticaria (CSU).

Summary

EudraCT number	2016-004624-35
Trial protocol	DE PL
Global end of trial date	25 October 2019

Results information

Result version number	v1 (current)
This version publication date	18 September 2020
First version publication date	18 September 2020

Trial information

Trial identification

Sponsor protocol code	GS39684
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03137069
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

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	25 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety and pharmacokinetics of GDC-0853.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

All Subjects were already treated with anti-histamines.

Evidence for comparator: -

Actual start date of recruitment	26 May 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	Canada: 64
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	134
EEA total number of subjects	29

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)	125
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 21 centers in 3 countries.

Pre-assignment

Screening details:

A total of 134 subjects were enrolled at 21 centers.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cohort 1: Placebo
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Arm description:

Subjects received matching placebo twice daily from Day 1 to 56.

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

Dosage and administration details:

Placebo matching GDC-0853 was administered.

Arm title	Cohort 1: GDC-0853 200mg BID
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Arm description:

Subjects received GDC-0853 200mg twice daily from Day 1 to 56.

Arm type	Experimental
Investigational medicinal product name	GDC-0853
Investigational medicinal product code	
Other name	fenebrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GDC-0853 was administered orally twice daily (BID) at a dose of 200mg.

Arm title	Cohort 2: Placebo
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Arm description:

Subjects received matching placebo up to twice daily from Day 1 to 56.

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

Dosage and administration details:

Placebo matching GDC-0853 was administered.

Arm title	Cohort 2: GDC-0853 50mg QD
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Arm description:

Subjects received GDC-0853 50mg once daily from Day 1 to 56.

Arm type	Experimental
Investigational medicinal product name	GDC-0853
Investigational medicinal product code	
Other name	fenebrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GDC-0853 was administered orally once daily (QD) at a dose of 50mg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching GDC-0853 was administered.

Arm title	Cohort 2: GDC-0853 150mg QD
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Arm description:

Subjects received GDC-0853 150mg once daily from Day 1 to 56.

Arm type	Experimental
Investigational medicinal product name	GDC-0853
Investigational medicinal product code	
Other name	fenebrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GDC-0853 was administered orally once daily (QD) at a dose of 150mg.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching GDC-0853 was administered.

Arm title	Cohort 2: GDC-0853 200mg BID
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Arm description:

Subjects received GDC-0853 200mg twice daily from Day 1 to 56.

Arm type	Experimental
Investigational medicinal product name	GDC-0853
Investigational medicinal product code	
Other name	fenebrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GDC-0853 was administered orally twice daily (BID) at a dose of 200mg.

Number of subjects in period 1	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: Placebo
Started	13	28	23
Completed	12	22	20
Not completed	1	6	3
Consent withdrawn by subject	1	2	2
Physician decision	-	-	-
Data Entry Error	-	-	-
Adverse event, non-fatal	-	3	1
Study Terminated by Sponsor	-	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Cohort 2: GDC-0853 50mg QD	Cohort 2: GDC-0853 150mg QD	Cohort 2: GDC-0853 200mg BID
Started	23	24	23
Completed	17	22	21
Not completed	6	2	2
Consent withdrawn by subject	2	-	-
Physician decision	1	-	-
Data Entry Error	1	-	-
Adverse event, non-fatal	1	-	1
Study Terminated by Sponsor	-	1	-
Protocol deviation	1	1	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Placebo
Reporting group description:	
Subjects received matching placebo twice daily from Day 1 to 56.	
Reporting group title	Cohort 1: GDC-0853 200mg BID
Reporting group description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56.	
Reporting group title	Cohort 2: Placebo
Reporting group description:	
Subjects received matching placebo up to twice daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 50mg QD
Reporting group description:	
Subjects received GDC-0853 50mg once daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 150mg QD
Reporting group description:	
Subjects received GDC-0853 150mg once daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 200mg BID
Reporting group description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56.	

Reporting group values	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: Placebo
Number of subjects	13	28	23
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	28	21
From 65-84 years	0	0	2
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	43.6	41.3	40.2
standard deviation	± 11.0	± 15.9	± 14.7
Sex: Female, Male			
Units:			
Female	11	22	17
Male	2	6	6
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	0	1	5
Not Hispanic or Latino	13	27	16

Not Stated	0	0	1
Unknown	0	0	1
Race/Ethnicity, Customized Units: Subjects			
Asian	0	3	4
Black or African American	1	1	1
White	10	24	18
Multiple	2	0	0

Reporting group values	Cohort 2: GDC-0853 50mg QD	Cohort 2: GDC-0853 150mg QD	Cohort 2: GDC-0853 200mg BID
Number of subjects	23	24	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	20	21
From 65-84 years	1	4	2
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	45.0	43.3	44.3
standard deviation	± 13.1	± 16.7	± 13.0
Sex: Female, Male Units:			
Female	18	20	16
Male	5	4	7
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	2	5	2
Not Hispanic or Latino	21	19	20
Not Stated	0	0	1
Unknown	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	3	1	4
Black or African American	1	0	2
White	19	23	16
Multiple	0	0	1

Reporting group values	Total		
Number of subjects	134		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	125		
From 65-84 years	9		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	104		
Male	30		
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	15		
Not Hispanic or Latino	116		
Not Stated	2		
Unknown	1		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	15		
Black or African American	6		
White	110		
Multiple	3		

End points

End points reporting groups

Reporting group title	Cohort 1: Placebo
Reporting group description:	
Subjects received matching placebo twice daily from Day 1 to 56.	
Reporting group title	Cohort 1: GDC-0853 200mg BID
Reporting group description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56.	
Reporting group title	Cohort 2: Placebo
Reporting group description:	
Subjects received matching placebo up to twice daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 50mg QD
Reporting group description:	
Subjects received GDC-0853 50mg once daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 150mg QD
Reporting group description:	
Subjects received GDC-0853 150mg once daily from Day 1 to 56.	
Reporting group title	Cohort 2: GDC-0853 200mg BID
Reporting group description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56.	
Subject analysis set title	Cohort 1: Placebo (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received matching placebo twice daily from Day 1 to 56.	
Subject analysis set title	Cohort 1: GDC-0853 200mg BID (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56.	
Subject analysis set title	Cohort 2: Placebo (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received matching placebo up to twice daily from Day 1 to 56. One subject in Cohort 2 was randomized into the Placebo arm (Cohort 2: Placebo) and received the Placebo treatment in the study. However due to a data entry error, this subject was inadvertently analysed in the (Cohort 2: GDC-0853 200 mg BID) arm in the Safety-evaluable population.	
Subject analysis set title	Cohort 2: GDC-0853 50mg QD (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received GDC-0853 50mg once daily from Day 1 to 56.	
Subject analysis set title	Cohort 2: GDC-0853 150mg QD (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received GDC-0853 150mg once daily from Day 1 to 56.	
Subject analysis set title	Cohort 2: GDC-0853 200mg BID (Safety-Evaluable Population)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received GDC-0853 200mg twice daily from Day 1 to 56. One subject in Cohort 2 was randomized into the Placebo arm (Cohort 2: Placebo) and received the Placebo treatment in the study. However due to a data entry error, this subject was inadvertently analysed in the (Cohort 2: GDC-0853 200 mg BID) arm in the Safety-evaluable population.	

Primary: Change from Baseline in the Urticaria Activity Score over 7 days (UAS7) at Day 57

End point title	Change from Baseline in the Urticaria Activity Score over 7 days (UAS7) at Day 57
End point description: The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. The maximum UAS7 value is 42. A higher score indicates worse disease. A negative change score (Day 57 score minus Baseline score) indicates improvement. This was assessed in the Modified Intent-To-Treat (mITT) Population defined as all subjects who received at least one dose of study treatment grouped for analysis according to the treatment arm to which they were randomized.	
End point type	Primary
End point timeframe: Baseline and Day 57	

End point values	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: Placebo	Cohort 2: GDC-0853 50mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	22	20	19
Units: Score on a Scale				
arithmetic mean (standard deviation)	-19.16 (± 13.49)	-24.05 (± 9.74)	-11.25 (± 10.81)	-15.69 (± 14.25)

End point values	Cohort 2: GDC-0853 150mg QD	Cohort 2: GDC-0853 200mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Score on a Scale				
arithmetic mean (standard deviation)	-17.05 (± 10.19)	-21.80 (± 14.80)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo v Cohort 1: GDC-0853 200mg BID
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	> 0.0559
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.02

Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.01
upper limit	-1.03

Notes:

[1] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 50mg QD
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	> 0.8892
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.51
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.6
upper limit	5.58

Notes:

[2] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 150mg QD
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	> 0.0717
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.29
upper limit	-0.57

Notes:

[3] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 200mg BID

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	> 0.0097
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-9.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.5
upper limit	-3.55

Notes:

[4] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Secondary: Percentage of Subjects who are Well-Controlled (UAS7 ≤ 6)

End point title	Percentage of Subjects who are Well-Controlled (UAS7 ≤ 6)
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End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. The maximum UAS7 value is 42. A higher score indicates worse disease. Subjects with UAS7 score ≤6 are considered well controlled. This was assessed in the Modified Intent-To-Treat (mITT) Population defined as all subjects who received at least one dose of study treatment grouped for analysis according to the treatment arm to which they were randomized.

End point type	Secondary
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End point timeframe:

Day 57

End point values	Cohort 1: Placebo	Cohort 1: GDC- 0853 200mg BID	Cohort 2: Placebo	Cohort 2: GDC- 0853 50mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	28	23	23
Units: Percentage of Participants				
number (not applicable)	30.8	57.1	21.7	34.8

End point values	Cohort 2: GDC- 0853 150mg QD	Cohort 2: GDC- 0853 200mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: Percentage of Participants				
number (not applicable)	45.8	56.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo v Cohort 1: GDC-0853 200mg BID
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	> 0.1087
Method	Cochran-Mantel-Haenszel

Notes:

[5] - Stratified by region

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 50mg QD
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	> 0.3418
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Stratified by region

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 150mg QD
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	> 0.0459
Method	Cochran-Mantel-Haenszel

Notes:

[7] - Stratified by region

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 200mg BID
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	> 0.019
Method	Cochran-Mantel-Haenszel

Notes:

[8] - Stratified by region

Secondary: Change from Baseline in the UAS7 at Day 29

End point title	Change from Baseline in the UAS7 at Day 29
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End point description:

The Urticaria Activity Score (UAS) is a composite, diary-recorded score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours (twice daily). The daily UAS is calculated as the average of the morning and evening scores. The UAS7 is the weekly sum of the daily UAS, which is the composite score of the intensity of pruritus and the number of wheals. The maximum UAS7 value is 42. A higher score indicates worse disease. A negative change score (Day 29 score minus Baseline score) indicates

improvement. This was assessed in the Modified Intent-To-Treat (mITT) Population defined as all subjects who received at least one dose of study treatment grouped for analysis according to the treatment arm to which they were randomized.

End point type	Secondary
End point timeframe:	
Baseline and Day 29	

End point values	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: Placebo	Cohort 2: GDC-0853 50mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	24	21	19
Units: Score on a Scale				
arithmetic mean (standard deviation)	-9.69 (± 10.70)	-22.15 (± 10.33)	-9.05 (± 9.82)	-16.97 (± 14.31)

End point values	Cohort 2: GDC-0853 150mg QD	Cohort 2: GDC-0853 200mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	21		
Units: Score on a Scale				
arithmetic mean (standard deviation)	-13.75 (± 12.93)	-21.69 (± 16.22)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1: Placebo v Cohort 1: GDC-0853 200mg BID
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	> 0.001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-12.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.94
upper limit	-6.82

Notes:

[9] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 50mg QD

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	> 0.4565
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.11
upper limit	3.46

Notes:

[10] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 150mg QD
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	> 0.1711
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-5.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.1
upper limit	1.03

Notes:

[11] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2: Placebo v Cohort 2: GDC-0853 200mg BID
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	> 0.005
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	-10.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.97
upper limit	-4.56

Notes:

[12] - Covariates included were region, treatment group, visit, and visit by treatment group interaction

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)
End point description:	
An Adverse Event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. This was assessed in the Safety-evaluable population defined as all subjects who received at least one dose of study drug with subjects grouped according to their actual treatment.	
End point type	Secondary
End point timeframe:	
Baseline up until 4 weeks after the last dose of study drug (up to 2 years, 5 months).	

End point values	Cohort 1: Placebo (Safety-Evaluable Population)	Cohort 1: GDC-0853 200mg BID (Safety-Evaluable Population)	Cohort 2: Placebo (Safety-Evaluable Population)	Cohort 2: GDC-0853 50mg QD (Safety-Evaluable Population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	28	22	23
Units: Percentage of Subjects				
number (not applicable)	61.5	71.4	54.5	60.9

End point values	Cohort 2: GDC-0853 150mg QD (Safety-Evaluable Population)	Cohort 2: GDC-0853 200mg BID (Safety-Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: Percentage of Subjects				
number (not applicable)	66.7	58.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of fenebrutinib (GDC-0853) at specified timepoints

End point title	Plasma Concentrations of fenebrutinib (GDC-0853) at specified timepoints ^[13]
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End point description:

Plasma Concentration Data for fenebrutinib (GDC-0853) will be tabulated and summarised by visits. Descriptive summary statistics for Arithmetic Mean and Standard Deviation will be presented. This was assessed in the PK-evaluable population defined as all subjects who received at least one dose of fenebrutinib (GDC-0853) and had at least 1 evaluable post-dose PK sample. Subjects who received incorrect therapy different from the intended therapy were summarized in the group according to the therapy actually received. Please note that the Placebo Cohorts were not evaluated for this Outcome Measure. 999 = Not Estimable.

End point type	Secondary
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End point timeframe:

Baseline up until 4 weeks after the last dose of study drug (up to 2 years, 5 months).

Notes:

[13] - 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 Placebo Cohorts were not evaluated for PK Analysis.

End point values	Cohort 1: GDC-0853 200mg BID	Cohort 2: GDC-0853 50mg QD	Cohort 2: GDC-0853 150mg QD	Cohort 2: GDC-0853 200mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	23	24	23
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	999 (± 999)	999 (± 999)	999 (± 999)	999 (± 999)
Day 8	378 (± 389)	38.5 (± 36.9)	178 (± 237)	424 (± 385)
Day 57	283 (± 315)	19.6 (± 26.3)	24.7 (± 17.7)	219 (± 293)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up until 4 weeks after the last dose of study drug (up to 2 years, 5 months).

Adverse event reporting additional description:

One subject in Cohort 2 was randomized into the Placebo arm (Cohort 2: Placebo) and received the Placebo treatment in the study. However due to a data entry error, this subject was inadvertently analysed in the (Cohort 2: GDC-0853 200 mg BID) arm in the Safety-evaluable population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Cohort 1: Placebo
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Reporting group description:

Subjects received matching placebo twice daily from Day 1 to 56.

Reporting group title	Cohort 1: GDC-0853 200mg BID
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Reporting group description:

Subjects received GDC-0853 200mg twice daily from Day 1 to 56.

Reporting group title	Cohort 2: GDC-0853 50mg QD
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Reporting group description:

Subjects received GDC-0853 50mg once daily from Day 1 to 56.

Reporting group title	Cohort 2: Placebo
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Reporting group description:

Subjects received matching placebo up to twice daily from Day 1 to 56.

Reporting group title	Cohort 2: GDC-0853 200mg BID
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Reporting group description:

Subjects received GDC-0853 200mg twice daily from Day 1 to 56.

Reporting group title	Cohort 2: GDC-0853 150mg QD
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Reporting group description:

Subjects received GDC-0853 150mg once daily from Day 1 to 56.

Serious adverse events	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: GDC-0853 50mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	3 / 28 (10.71%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 13 (0.00%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 13 (0.00%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PERIORBITAL CELLULITIS			
subjects affected / exposed	0 / 13 (0.00%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2: Placebo	Cohort 2: GDC-0853 200mg BID	Cohort 2: GDC-0853 150mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (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
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (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
Infections and infestations			
PERIORBITAL CELLULITIS			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (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

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

Non-serious adverse events	Cohort 1: Placebo	Cohort 1: GDC-0853 200mg BID	Cohort 2: GDC-0853 50mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)	16 / 28 (57.14%)	7 / 23 (30.43%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 13 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 13 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
WEIGHT DECREASED			
subjects affected / exposed	1 / 13 (7.69%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
BONE CONTUSION			
subjects affected / exposed	1 / 13 (7.69%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
CONTUSION			
subjects affected / exposed	0 / 13 (0.00%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
INJURY			
subjects affected / exposed	1 / 13 (7.69%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 13 (7.69%)	2 / 28 (7.14%)	0 / 23 (0.00%)
occurrences (all)	1	2	0
HEADACHE			
subjects affected / exposed	3 / 13 (23.08%)	4 / 28 (14.29%)	0 / 23 (0.00%)
occurrences (all)	3	5	0
General disorders and administration site conditions			
CHILLS			
subjects affected / exposed	1 / 13 (7.69%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
FATIGUE			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 28 (3.57%) 1	0 / 23 (0.00%) 0
FEELING ABNORMAL subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 28 (0.00%) 0	0 / 23 (0.00%) 0
Eye disorders VISION BLURRED subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 28 (0.00%) 0	0 / 23 (0.00%) 0
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 28 (3.57%) 1	0 / 23 (0.00%) 0
NAUSEA subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 28 (7.14%) 2	1 / 23 (4.35%) 1
Skin and subcutaneous tissue disorders CHRONIC SPONTANEOUS URTICARIA subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 28 (7.14%) 3	1 / 23 (4.35%) 2
URTICARIA subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	5 / 28 (17.86%) 5	3 / 23 (13.04%) 3
Musculoskeletal and connective tissue disorders BACK PAIN subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 28 (0.00%) 0	1 / 23 (4.35%) 1
Infections and infestations EYE INFECTION subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 28 (0.00%) 0	0 / 23 (0.00%) 0
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3	7 / 28 (25.00%) 9	3 / 23 (13.04%) 3
TOOTH INFECTION			

subjects affected / exposed	1 / 13 (7.69%)	0 / 28 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 13 (0.00%)	1 / 28 (3.57%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 13 (0.00%)	0 / 28 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1

Non-serious adverse events	Cohort 2: Placebo	Cohort 2: GDC-0853 200mg BID	Cohort 2: GDC-0853 150mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 22 (31.82%)	12 / 24 (50.00%)	13 / 24 (54.17%)
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 22 (0.00%)	3 / 24 (12.50%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 22 (0.00%)	2 / 24 (8.33%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
WEIGHT DECREASED			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
BONE CONTUSION			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
CONTUSION			
subjects affected / exposed	0 / 22 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
INJURY			
subjects affected / exposed	0 / 22 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
DIZZINESS			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 24 (4.17%) 1	0 / 24 (0.00%) 0
HEADACHE subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	3 / 24 (12.50%) 3	1 / 24 (4.17%) 1
General disorders and administration site conditions CHILLS subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
FATIGUE subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
FEELING ABNORMAL subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Eye disorders VISION BLURRED subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
NAUSEA subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 24 (8.33%) 2	2 / 24 (8.33%) 2
Skin and subcutaneous tissue disorders CHRONIC SPONTANEOUS URTICARIA subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 24 (0.00%) 0	2 / 24 (8.33%) 3
URTICARIA subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	5 / 24 (20.83%) 5	4 / 24 (16.67%) 4
Musculoskeletal and connective tissue disorders BACK PAIN			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Infections and infestations			
EYE INFECTION			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
NASOPHARYNGITIS			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	3 / 24 (12.50%) 4	3 / 24 (12.50%) 4
TOOTH INFECTION			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 24 (8.33%) 2	0 / 24 (0.00%) 0
URINARY TRACT INFECTION			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 24 (4.17%) 1	2 / 24 (8.33%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2017	Following updates were made: [1] Addition of a dose-ranging cohort (Cohort 2) gated on the basis of results from an interim analysis of Cohort 1 and language updated throughout the protocol to include the additional cohort accordingly; [2] Updates to background information on GDC-0853; [3] Clarification to exploratory biomarker objectives and endpoints; [4] Addition of the collection and storage of a blood sample for possible future DNA analyses; [5] Clarification to method of randomization; [6] Updating of reporting of the term "sudden death" to also require the presumed cause of death; [7] Clarification to event reporting for hospitalization; [8] Addition of content from previous protocol clarification letters and [9] Updating of Informed Consent Forms to reflect changes in the Protocol.
09 August 2018	Following updates were made: [1] Updating of name of study drug from GDC-0853 to fenebrutinib throughout the document; [2] Update to Medical Monitor contact; [3] General enrolment update; [4] Clarification regarding use of rescue medication and contradictory language regarding tubal ligation; [5] Update to Inclusion Criteria; [6] Clarification of fasting before morning clinic visits; [7] Update to Bilastine dose range; [8] Clarification regarding effect of ethinyl estradiol with fenebrutinib, use of prohibited therapies, corticosteroids for exacerbations and eligibility criteria for re-screening; [9] Clarification of the UAS7 definition and [10] Additional information regarding Whole Genome Sequencing (WGS), Infections, Bleeding and Gastrointestinal effects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruitment was stopped after an interim analysis of Cohort 2 based on pre-specified internal criteria.

Notes: