Clinical trial results:
A Phase II Open-Label Extension Study of Patients Previously Enrolled in Study GA29350 to Evaluate the Long-Term Safety and Efficacy of GDC-0853 in Patients With Moderate to Severe Rheumatoid Arthritis

Summary

EudraCT number	2016-000498-19
Trial protocol	BG
Global end of trial date	17 July 2019

Results information

Result version number	v1 (current)
This version publication date	25 July 2020
First version publication date	25 July 2020

Trial information

Trial identification

Sponsor protocol code	GA30067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02983227
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	17 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term safety and efficacy of GDC-0853.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 60
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Brazil: 51
Country: Number of subjects enrolled	Colombia: 22
Country: Number of subjects enrolled	Mexico: 36
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Serbia: 36
Country: Number of subjects enrolled	Ukraine: 135
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	496
EEA total number of subjects	62

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)	442
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 138 centers in 19 countries.

Pre-assignment

Screening details:

496 subjects were enrolled into this OLE study and were included in the ITT and Safety populations.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GDC-0853 (200mg BID) Cohort 1

Arm description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo.

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

Dosage and administration details:

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

Arm title	GDC-0853 (200mg BID) Cohort 2

Arm description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo.

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

Dosage and administration details:

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

Number of subjects in period 1	GDC-0853 (200mg BID) Cohort 1	GDC-0853 (200mg BID) Cohort 2
Started	410	86
Completed	351	72
Not completed	59	14
Adverse event, serious fatal	3	-
Physician decision	3	1
Consent withdrawn by subject	19	8
Adverse event, non-fatal	21	3
Multiple Reasons	2	1
Lost to follow-up	3	-
Lack of efficacy	8	1

Baseline characteristics

Reporting groups	
Reporting group title	GDC-0853 (200mg BID) Cohort 1
Reporting group description:	
Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo.	
Reporting group title	GDC-0853 (200mg BID) Cohort 2
Reporting group description:	
Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo.	

Reporting group values	GDC-0853 (200mg BID) Cohort 1	GDC-0853 (200mg BID) Cohort 2	Total
Number of subjects	410	86	496
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)	371	71	442
From 65-84 years	39	15	54
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	49.9	53.5	
standard deviation	± 11.7	± 12.5	-
Sex: Female, Male Units:			
Female	334	64	398
Male	76	22	98
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	136	30	166
Not Hispanic or Latino	267	56	323
Not Stated	2	0	2
Unknown	5	0	5
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska native	27	11	38
Asian	1	0	1

Black or African American	7	2	9
Multiple	7	2	9
Unknown	3	0	3
White	365	71	436

End points

End points reporting groups

Reporting group title	GDC-0853 (200mg BID) Cohort 1

Reporting group description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo.

Reporting group title	GDC-0853 (200mg BID) Cohort 2

Reporting group description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo.

Subject analysis set title	GDC-0853 (200mg BID) Cohort 1 (PK-Evaluable Population)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo. The PK-Evaluable population was defined as all subjects that received any fenebrutinib/GDC-0853 and had sufficient data to enable estimation of key PK parameters. Subjects who received incorrect therapy different from the intended therapy were summarized in the group according to the therapy actually received.

Subject analysis set title	GDC-0853 (200mg BID) Cohort 2 (PK-Evaluable Population)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo. The PK-Evaluable population was defined as all participants that received any fenebrutinib/GDC-0853 and had sufficient data to enable estimation of key PK parameters. Participants who received incorrect therapy different from the intended therapy were summarized in the group according to the therapy actually received.

Subject analysis set title	GDC-0853 (200mg BID) Cohort 1 (ITT Population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo. The Intent-To-Treat (ITT) Population was defined as all eligible subjects enrolled in this OLE study.

Subject analysis set title	GDC-0853 (200mg BID) Cohort 2 (ITT Population)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo. The Intent-To-Treat (ITT) Population was defined as all eligible subjects enrolled in this OLE study.

Primary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)[1]

End point description:

An Adverse Event (AE) was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events.

End point type	Primary

End point timeframe:

Day 1 up until 8 weeks after the last dose of study drug (up to 1 year, 2 months)

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: No statistical analyses were performed, as this study has only 1 arm.

End point values	GDC-0853 (200mg BID) Cohort 1	GDC-0853 (200mg BID) Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	410	86		
Units: Percentage				
number (not applicable)	60.2	57.0		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Achieving American College of Rheumatology 50% (ACR50) Response at Week 52

End point title	Percentage of Subjects Achieving American College of Rheumatology 50% (ACR50) Response at Week 52[2]

End point description:

ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].

End point type	Primary

End point timeframe:

Week 52

Notes:

[2] - 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: No statistical analyses were performed, as this study has only 1 arm.

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage				
number (confidence interval 95%)	57.1 (52.28 to 61.86)	50.0 (39.43 to 60.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving ACR50 Response up to Week 12

End point title	Percentage of Subjects Achieving ACR50 Response up to Week 12

End point description:

ACR50 response is defined as a ≥ 50% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 12

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage				
number (confidence interval 95%)				
Week 4	37.1 (32.40 to 41.75)	29.1 (19.47 to 38.67)		
Week 8	42.4 (37.65 to 47.22)	34.9 (24.81 to 44.96)		
Week 12	45.6 (40.79 to 50.43)	39.5 (29.20 to 49.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) Response

End point description:

ACR20 response is defined as a ≥ 20% improvement (reduction) compared with baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate]

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage				
number (confidence interval 95%)				
Week 4	69.0 (64.55 to 73.50)	58.1 (47.71 to 68.57)		
Week 8	72.9 (68.63 to 77.23)	68.6 (58.80 to 78.41)		
Week 12	74.4 (70.17 to 78.62)	73.3 (63.90 to 82.61)		
Week 24	75.4 (71.20 to 79.54)	72.1 (62.61 to 81.57)		
Week 36	75.1 (70.94 to 79.31)	72.1 (62.61 to 81.57)		
Week 52	75.4 (71.20 to 79.54)	68.6 (58.80 to 78.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 70% (ACR70) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 70% (ACR70) Response

End point description:

ACR70 response is defined as a ≥ 70% improvement (reduction) compared with Baseline for both total

joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), as well as for three of the additional five ACR core set variables: Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain; Patient's Global Assessment of Disease Activity and Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity; Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do; and acute-phase reactant [either C-reactive protein or Erythrocyte Sedimentation Rate].

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage				
number (confidence interval 95%)				
Week 4	19.8 (15.90 to 23.61)	12.8 (5.73 to 19.85)		
Week 8	21.7 (17.72 to 25.70)	17.4 (9.42 to 25.46)		
Week 12	23.9 (19.77 to 28.03)	19.8 (11.35 to 28.18)		
Week 24	30.2 (25.80 to 34.69)	20.9 (12.33 to 29.53)		
Week 36	32.2 (27.67 to 36.72)	25.6 (16.36 to 34.80)		
Week 52	36.3 (31.69 to 41.00)	27.9 (18.43 to 37.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score Based on 28-Joints Count and C-Reactive Protein (3 Variables) (DAS28-3 CRP)

End point title	Disease Activity Score Based on 28-Joints Count and C-Reactive Protein (3 Variables) (DAS28-3 CRP)

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6. Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	406	86		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (C1, n=406; C2, n=86)	5.49 (± 0.85)	5.59 (± 0.90)		
Week 4 (C1, n=398; C2, n=83)	3.64 (± 1.11)	4.09 (± 1.19)		
Week 8 (C1, n=386; C2, n=84)	3.48 (± 1.06)	3.81 (± 1.15)		
Week 12 (C1, n=378; C2, n=83)	3.37 (± 1.09)	3.73 (± 1.11)		
Week 24 (C1, n=372; C2, n=82)	3.16 (± 1.05)	3.55 (± 1.18)		
Week 36 (C1, n=361; C2, n=79)	3.05 (± 1.05)	3.36 (± 1.06)		
Week 52 (C1, n=349; C2, n=71)	2.90 (± 1.03)	3.17 (± 1.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score Based on 28-Joints Count and C-Reactive Protein (4 Variables) (DAS28-4 CRP)

End point title	Disease Activity Score Based on 28-Joints Count and C-Reactive Protein (4 Variables) (DAS28-4 CRP)

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6. Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	391	86		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (C1, n=387; C2, n=86)	5.83 (± 0.88)	5.95 (± 0.94)		
Week 4 (C1, n=391; C2, n=83)	3.70 (± 1.19)	4.22 (± 1.34)		

Week 8 (C1, n=378; C2, n=84)	3.53 (± 1.13)	3.92 (± 1.25)		
Week 12 (C1, n=373; C2, n=83)	3.39 (± 1.14)	3.81 (± 1.21)		
Week 24 (C1, n=369; C2, n=82)	3.18 (± 1.13)	3.64 (± 1.27)		
Week 36 (C1, n=360; C2, n=79)	3.06 (± 1.14)	3.44 (± 1.21)		
Week 52 (C1, n=348; C2, n=71)	2.87 (± 1.09)	3.22 (± 1.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (3 Variables) (DAS28-3 ESR)

End point title	Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (3 Variables) (DAS28-3 ESR)

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6. Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	404	86		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Baseline (C1, n=404; C2, n=86)	6.17 (± 0.79)	6.38 (± 0.88)		
Week 4 (C1, n=397; C2, n=85)	4.25 (± 1.16)	4.80 (± 1.26)		
Week 8 (C1, n=389; C2, n=83)	4.04 (± 1.14)	4.51 (± 1.17)		
Week 12 (C1, n=381; C2, n=83)	3.89 (± 1.16)	4.40 (± 1.11)		
Week 24 (C1, n=375; C2, n=83)	3.65 (± 1.08)	4.15 (± 1.27)		
Week 36 (C1, n=361; C2, n=79)	3.46 (± 1.15)	3.96 (± 1.15)		
Week 52 (C1, n=347; C2, n=72)	3.35 (± 1.14)	3.74 (± 1.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (4 Variables) (DAS28-4 ESR)

End point title	Disease Activity Score Based on 28-Joints Count and Erythrocyte Sedimentation Rate (4 Variables) (DAS28-4 ESR)

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. DAS28 Remission is defined as a DAS28 score < 2.6. Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	390	86		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Baseline (C1, n=385; C2, n=86)	6.48 (± 0.85)	6.71 (± 0.96)		
Week 4 (C1, n=390; C2, n=85)	4.27 (± 1.25)	4.89 (± 1.41)		
Week 8 (C1, n=381; C2, n=83)	4.04 (± 1.23)	4.58 (± 1.29)		
Week 12 (C1, n=376; C2, n=83)	3.87 (± 1.23)	4.44 (± 1.25)		
Week 24 (C1, n=373; C2, n=83)	3.62 (± 1.16)	4.20 (± 1.37)		
Week 36 (C1, n=360; C2, n=79)	3.43 (± 1.24)	3.99 (± 1.30)		
Week 52 (C1, n=346; C2, n=72)	3.27 (± 1.20)	3.74 (± 1.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Remission Based on Disease Activity Score Based on 28-Joints Count (DAS28)

End point title	Percentage of Subjects With Remission Based on Disease Activity Score Based on 28-Joints Count (DAS28)

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage of Subjects				
number (not applicable)				
Week 4	8.8	7.0		
Week 8	10.7	8.1		
Week 12	13.9	8.1		
Week 24	17.8	14.0		
Week 36	22.4	11.6		
Week 52	25.6	23.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Low Disease Activity (LDA) Based on DAS28

End point title	Percentage of Subjects With Low Disease Activity (LDA) Based on DAS28

End point description:

The DAS28 score is a measure of the patient's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and the erythrocyte sedimentation rate (ESR) for a total possible score of 0 to approximately 10. Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. LDAS is defined as DAS28 ≤ 3.2.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	410	86		
Units: Percentage of Subjects				
number (not applicable)				
Week 4	20.0	12.8		
Week 8	21.2	17.4		
Week 12	26.6	12.8		
Week 24	33.7	27.9		

Week 36	38.3	29.1		
Week 52	42.2	29.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With ACR/EULAR Remission

End point title	Percentage of Subjects With ACR/EULAR Remission

End point description:

Assessed according to the Boolean based definition (tender joint count =<1, swollen joint count =<1, C-reactive Protein (CRP) =<1, and patient global assessment =<1). Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	401	86		
Units: Percentage of Subjects				
number (not applicable)				
Week 4 (C1, n=401; C2, n=86)	5.0	5.8		
Week 8 (C1, n=397; C2, n=85)	7.8	5.9		
Week 12 (C1, n=390; C2, n=83)	7.4	7.2		
Week 24 (C1, n=378; C2, n=83)	13.0	6.0		
Week 36 (C1, n=366; C2, n=79)	15.6	11.4		
Week 52 (C1, n=353; C2, n=75)	17.8	10.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI)

End point title	Change from Baseline in Simplified Disease Activity Index (SDAI)

End point description:

Simplified Disease Activity Index (SDAI) is the numerical sum of five outcome parameters: TJC and SJC (based on a 28-joint assessment), PtGA and PhGA (based on 0-10 cm VAS, where 0 = no disease activity and 10 = worst disease activity), and CRP. SDAI total score ranges from 0 (no disease activity) to 86 (maximal disease activity), where higher scores represents higher disease activity. The SDAI =< 3.3 indicates disease remission, > 3.4 to 11 indicates low disease activity, > 11 to 26 indicates

moderate disease activity, and > 26 indicates high disease activity. Number of subjects for whom data were actually collected is indicated for each time point. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	373	84		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=373; C2, n=83)	-24.36 (± 13.58)	-21.00 (± 13.49)		
Week 8 (C1, n=362; C2, n=84)	-26.17 (± 13.58)	-24.06 (± 13.57)		
Week 12 (C1, n=355; C2, n=83)	-27.91 (± 12.89)	-25.21 (± 13.37)		
Week 24 (C1, n=352; C2, n=82)	-29.61 (± 13.14)	-26.45 (± 14.17)		
Week 36 (C1, n=342; C2, n=79)	-30.47 (± 13.72)	-28.22 (± 14.16)		
Week 52 (C1, n=331; C2, n=71)	-31.69 (± 13.12)	-29.68 (± 13.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI)

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI)

End point description:

CDAI was derived as the sum of the following: tender joint count (TJC), swollen joint count (SJC), participant global assessment (PGA) of disease activity, and physician assessment of disease activity. TJC and SJC were taken as the number of tender and swollen joints, respectively, out of 28 assessed joints. PGA and physician assessment of disease activity were scored 0-100 millimeters (mm) and rounded to the nearest centimeter (cm) on a visual analog scale (VAS), where higher scores indicate greater perceived disease activity. The total CDAI score range was 0-76, where higher scores indicate increased disease activity. Change from baseline at a particular time point was calculated among patients with data available at both baseline and the time point of interest. Negative values indicate improvement/reduction in RA disease activity. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	374[3]	86[4]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=374; C2, n=86)	-23.41 (± 13.11)	-19.81 (± 13.15)		
Week 8 (C1, n=366; C2, n=84)	-25.14 (± 13.06)	-22.48 (± 12.59)		
Week 12 (C1, n=360; C2, n=83)	-26.82 (± 12.31)	-23.82 (± 12.37)		
Week 24 (C1, n=356; C2, n=83)	-28.52 (± 12.52)	-25.09 (± 13.18)		
Week 36 (C1, n=343; C2, n=79)	-29.40 (± 12.99)	-26.66 (± 12.98)		
Week 52 (C1, n=332; C2, n=72)	-30.61 (± 12.43)	-27.43 (± 13.43)		

Notes:

[3] - Number of subjects for whom data were actually collected is indicated for each time point.

[4] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tender/Painful Joint Count Based on 68 Joints

End point title	Change from Baseline in Tender/Painful Joint Count Based on 68 Joints

End point description:

Tender Joint Count: a total of 68 joints will be assessed for tenderness. Each joint is assessed for the presence/absence of tenderness. 68 joints are assessed for tenderness and joints are classified as tender/not tender giving a total possible tender joint count score of 0 to 68. A negative change from Baseline indicated improvement. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	406[5]	86[6]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=400; C2, n=86)	-15.02 (± 12.38)	-13.23 (± 12.27)		
Week 8 (C1, n=404; C2, n=86)	-16.11 (± 12.45)	-15.19 (± 12.59)		
Week 12 (C1, n=406; C2, n=86)	-16.55 (± 12.39)	-15.99 (± 12.03)		

Week 24 (C1, n=406; C2, n=86)	-17.96 (± 12.24)	-16.65 (± 11.35)		
Week 36 (C1, n=406; C2, n=86)	-18.48 (± 12.77)	-17.51 (± 11.60)		
Week 52 (C1, n=406; C2, n=86)	-18.70 (± 12.99)	-17.73 (± 11.88)		

Notes:

[5] - Number of subjects for whom data were actually collected is indicated for each time point.

[6] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Swollen Joint Count Based on 66 Joints

End point title	Change from Baseline in Swollen Joint Count Based on 66 Joints

End point description:

Swollen Joint Count: a total of 66 joints will be assessed for swelling. Each joint is assessed for the presence/absence of swelling. 66 joints were assessed for swelling and joints are classified as swollen/not swollen giving a total possible swollen joint count score of 0 to 66. A negative change from Baseline indicated improvement. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	406[7]	86[8]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=400; C2, n=86)	-10.20 (± 8.43)	-7.85 (± 6.71)		
Week 8 (C1, n=404; C2, n=86)	-10.95 (± 8.48)	-9.12 (± 6.65)		
Week 12 (C1, n=406; C2, n=86)	-11.40 (± 8.22)	-9.08 (± 6.84)		
Week 24 (C1, n=406; C2, n=86)	-11.93 (± 8.33)	-9.86 (± 6.61)		
Week 36 (C1, n=406; C2, n=86)	-12.15 (± 8.57)	-9.98 (± 6.96)		
Week 52 (C1, n=406; C2, n=86)	-12.17 (± 8.55)	-9.59 (± 8.78)		

Notes:

[7] - Number of subjects for whom data were actually collected is indicated for each time point.

[8] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient's Assessment of Arthritis Pain, Using Visual Analog Scale (VAS) Score

End point title	Change from Baseline in Patient's Assessment of Arthritis Pain, Using Visual Analog Scale (VAS) Score

End point description:

Patient's Assessment of Pain over the previous 24 hours: using a Visual Analog Scale (VAS) left end of the line 0=no pain to right end of the line 100=unbearable pain. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	371[9]	86[10]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=371; C2, n=86)	-30.62 (± 26.60)	-26.34 (± 25.98)		
Week 8 (C1, n=365; C2, n=84)	-32.57 (± 26.77)	-27.21 (± 23.36)		
Week 12 (C1, n=354; C2, n=83)	-35.68 (± 26.44)	-29.49 (± 26.70)		
Week 24 (C1, n=356; C2, n=83)	-37.19 (± 26.85)	-30.30 (± 26.42)		
Week 36 (C1, n=343; C2, n=79)	-39.50 (± 27.20)	-33.14 (± 27.22)		
Week 52 (C1, n=330; C2, n=72)	-42.40 (± 26.22)	-38.21 (± 26.37)		

Notes:

[9] - Number of subjects for whom data were actually collected is indicated for each time point.

[10] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Patient's Global Assessment of Arthritis, Using VAS Score

End point title	Change from Baseline in Patient's Global Assessment of Arthritis, Using VAS Score

End point description:

Participant-assessed arthritis pain was scored on a 100-mm VAS, where the distance from 0 mm represented the participant's self evaluation of arthritis pain (0 mm=none; 100 mm=very severe). Change from baseline at a particular time point was calculated among patients with data available at both baseline and the time point of interest, where negative change indicated a decrease in participant-assessed arthritis pain. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	375[11]	86[12]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=375; C2, n=86)	-30.21 (± 27.47)	-26.03 (± 24.50)		
Week 8 (C1, n=366; C2, n=84)	-32.67 (± 26.85)	-28.79 (± 23.07)		
Week 12 (C1, n=360; C2, n=83)	-35.63 (± 26.19)	-31.16 (± 25.32)		
Week 24 (C1, n=356; C2, n=83)	-36.94 (± 27.23)	-31.76 (± 25.09)		
Week 36 (C1, n=343; C2, n=79)	-39.40 (± 26.77)	-33.73 (± 25.82)		
Week 52 (C1, n=332; C2, n=72)	-42.91 (± 25.90)	-36.58 (± 24.74)		

Notes:

[11] - Number of subjects for whom data were actually collected is indicated for each time point.

[12] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Physician's Global Assessment of Arthritis, Using VAS Score

End point title	Change from Baseline in Physician's Global Assessment of Arthritis, Using VAS Score

End point description:

Physician's assessment of participant's disease activity was scored on a 100-mm VAS, where the distance from 0 mm represented the physician's assessment of the participant's disease activity (0 mm=very good; 100 mm=very poor). Change from baseline at a particular time point was calculated among patients with data available at both baseline and the time point of interest, where negative change from baseline indicated an improvement in physician-assessed disease activity. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	399[13]	86[14]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				

Week 4 (C1, n=399; C2, n=86)	-37.07 (± 20.75)	-30.65 (± 24.09)		
Week 8 (C1, n=390; C2, n=84)	-39.29 (± 20.30)	-35.32 (± 22.36)		
Week 12 (C1, n=383; C2, n=83)	-42.23 (± 20.20)	-37.37 (± 22.14)		
Week 24 (C1, n=376; C2, n=83)	-44.40 (± 20.94)	-41.11 (± 23.86)		
Week 36 (C1, n=362; C2, n=79)	-45.52 (± 20.76)	-43.13 (± 24.14)		
Week 52 (C1, n=350; C2, n=72)	-48.57 (± 19.99)	-44.81 (± 23.85)		

Notes:

[13] - Number of subjects for whom data were actually collected is indicated for each time point.

[14] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-Reactive Protein (CRP) Levels

End point title	Change from Baseline in C-Reactive Protein (CRP) Levels

End point description:

C-reactive protein is a biological marker of inflammation and is measured in milligrams per decilitre (mg/dL). (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	398[15]	84[16]		
Units: (mg/dL)				
arithmetic mean (standard deviation)				
Week 4 (C1, n=398; C2, n=83)	-0.95 (± 2.18)	-1.09 (± 3.10)		
Week 8 (C1, n=386; C2, n=84)	-1.02 (± 2.41)	-1.58 (± 2.60)		
Week 12 (C1, n=378; C2, n=83)	-1.03 (± 2.21)	-1.40 (± 3.38)		
Week 24 (C1, n=372; C2, n=82)	-1.03 (± 2.48)	-1.46 (± 2.99)		
Week 36 (C1, n=361; C2, n=79)	-1.11 (± 2.44)	-1.56 (± 3.04)		
Week 52 (C1, n=349; C2, n=71)	-1.12 (± 2.55)	-1.81 (± 2.75)		

Notes:

[15] - Number of subjects for whom data were actually collected is indicated for each time point.

[16] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Assessment Questionnaire-Disability

Index (HAQ-DI) Score

End point title	Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score

End point description:

The Stanford Health Assessment Questionnaire disability index is a patient-reported outcome used to assess difficulty in performing activities of daily living. It consists of 20 questions referring to eight domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. To respond to each question, a four-level response with higher scores showing larger functional limitations, was chosen. Scoring is as follows with respect to performance of participant's everyday activities: 0 (equals)=without difficulties; 1= with some difficulties; 2=with great difficulties; and 3=unable to perform these actions at all. The composite HAQ-DI score is the mean of the eight domain scores and the score ranges from 0 (no functional impairment) to 3 (maximum functional impairment). A negative change from baseline indicates improvement. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 24, 36 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	360[17]	81[18]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 (C1, n=360; C2, n=81)	-0.70 (± 0.64)	-0.55 (± 0.56)		
Week 8 (C1, n=358; C2, n=80)	-0.77 (± 0.65)	-0.59 (± 0.62)		
Week 12 (C1, n=358; C2, n=78)	-0.80 (± 0.67)	-0.60 (± 0.59)		
Week 24 (C1, n=349; C2, n=78)	-0.83 (± 0.66)	-0.63 (± 0.58)		
Week 36 (C1, n=338; C2, n=74)	-0.89 (± 0.63)	-0.62 (± 0.66)		
Week 52 (C1, n=323; C2, n=70)	-0.98 (± 0.64)	-0.69 (± 0.62)		

Notes:

[17] - Number of subjects for whom data were actually collected is indicated for each time point.

[18] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 36-Item Short-Form Health Survey (SF-36) Version 2.0 (V2) Scores for Physical and Mental Components

End point title	Change from Baseline in 36-Item Short-Form Health Survey (SF-36) Version 2.0 (V2) Scores for Physical and Mental Components

End point description:

The 36-Item Short Form Health Survey (SF-36v2) is a questionnaire used to assess functional health and well-being and consists of eight domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health. The SF-36v2 is summarized into Physical Component Summary (PCS) (Phys Comp Sc chnge) and Mental Component Summary (MCS) (Ment Comp Sc chnge) scores. The PCS and MCS scores range from 0 to 100, with 0=worst score (or quality of life) and 100=best score. A positive change from baseline indicates improvement. (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 12, 24 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	356[19]	83[20]		
Units: Number on a Scale				
arithmetic mean (standard deviation)				
Week 12 (Phys Comp Sc chnge) (C1, n=356; C2, n=83)	11.35 (± 9.13)	8.22 (± 8.73)		
Week 12 (Ment Comp Sc chnge) (C1, n=356; C2, n=83)	6.52 (± 12.98)	4.74 (± 11.53)		
Week 24 (Phys Comp Sc chnge) (C1, n=350; C2, n=80)	12.31 (± 9.12)	8.28 (± 8.53)		
Week 24 (Ment Comp Sc chnge) (C1, n=350; C2, n=80)	6.63 (± 13.23)	6.08 (± 11.76)		
Week 52 (Phys Comp Sc chnge) (C1, n=330; C2, n=72)	13.89 (± 9.32)	10.42 (± 8.94)		
Week 52 (Ment Comp Sc chnge) (C1, n=330; C2, n=72)	7.00 (± 13.81)	6.77 (± 11.60)		

Notes:

[19] - Number of subjects for whom data were actually collected is indicated for each time point.

[20] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Score

End point description:

The FACIT-Fatigue Scale consists of 13 items designed to measure the degree of fatigue experienced by the patient in the previous 7 days. For each question, there are five possible responses: 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), 4 (very much). A total fatigue score is calculated by summing all items, and possible total scores range from 0 (maximum fatigue) to 52 (no fatigue). A positive change from baseline indicates an improvement in the patient's fatigue (less fatigue). (C1, n=X; C2, n=X) refers to number of subjects analysed in Cohorts 1 and 2 (C1/C2) at each timepoint.

End point type	Secondary

End point timeframe:

Weeks 12, 24 and 52

End point values	GDC-0853 (200mg BID) Cohort 1 (ITT Population)	GDC-0853 (200mg BID) Cohort 2 (ITT Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	350[21]	83[22]		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 12 (C1, n=350; C2, n=83)	11.44 (± 10.36)	9.28 (± 8.51)		
Week 24 (C1, n=347; C2, n=80)	11.74 (± 10.75)	10.41 (± 8.51)		
Week 52 (C1, n=327; C2, n=72)	12.87 (± 10.58)	10.87 (± 9.25)		

Notes:

[21] - Number of subjects for whom data were actually collected is indicated for each time point.

[22] - Number of subjects for whom data were actually collected is indicated for each time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Time Curve (AUC) of GDC-0853 at Steady State (AUC,ss)

End point title	Area Under the Concentration Time Curve (AUC) of GDC-0853 at Steady State (AUC,ss)

End point description:

Population PK model estimated AUC of GDC-0853 at steady-state. AUC was measured in Nanograms (ng) per millilitre (mL)*hour (hr).

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Weeks 0 (Day 1), 4, 12, 24, 36, and 52/early termination

End point values	GDC-0853 (200mg BID) Cohort 1 (PK-Evaluable Population)	GDC-0853 (200mg BID) Cohort 2 (PK-Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	388	81		
Units: Ng/mL*(hr)				
arithmetic mean (standard deviation)	13400 (± 6930)	15600 (± 7850)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration of GDC-0853 at Steady State (Ctrough,ss)

End point title	Minimum Observed Plasma Concentration of GDC-0853 at

	Steady State (Ctrough,ss)

End point description:

Population PK model estimated minimal plasma concentration (Ctrough) of GDC-0853 at steady-state (ss).

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Weeks 0 (Day 1), 4, 12, 24, 36, and 52/early termination

End point values	GDC-0853 (200mg BID) Cohort 1 (PK-Evaluable Population)	GDC-0853 (200mg BID) Cohort 2 (PK-Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	388	81		
Units: ng/mL				
arithmetic mean (standard deviation)	387 (± 244)	467 (± 285)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Decay Half-Life of GDC-0853 at Steady State (t1/2,ss)

End point title	Plasma Decay Half-Life of GDC-0853 at Steady State (t1/2,ss)

End point description:

Population PK model estimated plasma decay half life of GDC-0853 at steady-state.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Weeks 0 (Day 1), 4, 12, 24, 36, and 52/early termination

End point values	GDC-0853 (200mg BID) Cohort 1 (PK-Evaluable Population)	GDC-0853 (200mg BID) Cohort 2 (PK-Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	388	81		
Units: hr				
arithmetic mean (standard deviation)	7.94 (± 3.16)	9.01 (± 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Oral Clearance of GDC-0853 at Steady State (CL/F,ss)

End point title	Apparent Oral Clearance of GDC-0853 at Steady State (CL/F,ss)

End point description:

Population PK model estimated apparent oral clearance of GDC-0853 at steady-state.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour) on Weeks 0 (Day 1), 4, 12, 24, 36, and 52/early termination

End point values	GDC-0853 (200mg BID) Cohort 1 (PK-Evaluable Population)	GDC-0853 (200mg BID) Cohort 2 (PK-Evaluable Population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	388	81		
Units: L/hr				
arithmetic mean (standard deviation)	39.5 (± 12.6)	35.3 (± 10.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up until 8 weeks after the last dose of study drug (up to 1 year, 2 months).

Adverse event reporting additional description:

The Safety-evaluable population was defined as all subjects who received any study drug and had at least one assessment of safety. AEs that were entered into the database at the time of the database lock were included in the AE analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	GDC-0853 (200mg BID) Cohort 2

Reporting group description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 2 of Study GA29350. Cohort 2 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to one or two tumor necrosis factor (TNF) inhibitors and methotrexate (MTX) therapy, and then randomized to 12 weeks of GDC-0853 (200 mg BID) or placebo.

Reporting group title	GDC-0853 (200mg BID) Cohort 1

Reporting group description:

Subjects received GDC-0853 orally twice daily (BID) for 52 weeks, after completing 12 weeks in Cohort 1 of Study GA29350. Cohort 1 subjects in GA29350 were enrolled with moderate to severe active Rheumatoid Arthritis (RA) and an inadequate response to previous methotrexate (MTX) therapy and then randomized to 12 weeks of GDC-0853 (50 mg daily, 150 mg daily, or 200 mg BID), adalimumab, or placebo.

Serious adverse events	GDC-0853 (200mg BID) Cohort 2	GDC-0853 (200mg BID) Cohort 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 86 (4.65%)	26 / 410 (6.34%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 86 (1.16%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG CARCINOMA CELL TYPE UNSPECIFIED STAGE IV			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
VAGINAL HAEMORRHAGE			
subjects affected / exposed	0 / 86 (0.00%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
HEAD INJURY			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 86 (1.16%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE INJURIES			

subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 86 (1.16%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VERTEBROBASILAR INSUFFICIENCY			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
IRON DEFICIENCY ANAEMIA			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLAMMATORY BOWEL DISEASE			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 86 (0.00%)	2 / 410 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
URETEROLITHIASIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRITIS			

subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROTISING SOFT TISSUE INFECTION			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 86 (1.16%)	0 / 410 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			

subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	0 / 86 (0.00%)	1 / 410 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	GDC-0853 (200mg BID) Cohort 2	GDC-0853 (200mg BID) Cohort 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 86 (4.65%)	22 / 410 (5.37%)	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 86 (4.65%)	22 / 410 (5.37%)	
occurrences (all)	7	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	Following updates were made: [1] Updating of background and nonclinical experience with GDC-0853; [2] Clarification of secondary efficacy objective to assess Boolean- and SDAI-based remission; [3] Removal of Week 2 assessments; [4] Updating of rationale for GDC-0853 dose and schedule; [5] Clarification of inclusion criterion for completion of Parent Study GA29350; [6] Updating of storage temperature for GDC-0853; [7] Clarification of Dosing for Day 1; [8] Updating of Labeling of dates on the blister wallets and bottles; [9] Removal of male-specific Informed Consent; [10] Clarification of method of patient-reported (via electronic device) and clinician-reported outcomes (paper based); [11] Addition of Updated nonclinical information and [12] Updating of Management guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported