



Clinical trial results:

A Phase 2, Blinded, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of GS-4875 in Subjects with Moderately to Severely Active Ulcerative Colitis

Summary

EudraCT number	2019-001430-33
Trial protocol	AT FR GB DE PL BE IT
Global end of trial date	14 December 2021

Results information

Result version number	v1 (current)
This version publication date	14 August 2022
First version publication date	14 August 2022

Trial information

Trial identification

Sponsor protocol code	GS-US-365-4237
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04130919
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2021
Global end of trial reached?	Yes
Global end of trial date	14 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy of tilpisertib (formerly GS-4875) compared with placebo control in achieving clinical remission per modified Mayo Clinic Score (MCS) in adults with moderately to severely active ulcerative colitis (UC).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	19
EEA total number of subjects	3

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)	15
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Europe and the United States.

Pre-assignment

Screening details:

32 participants were screened.

Period 1

Period 1 title	Blinded Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tilpisertib 300 mg (Blinded Treatment Phase)

Arm description:

Tilpisertib 300 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per Modified Mayo Clinic score (MCS) at Week 10, continued to receive tilpisertib 300 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Arm type	Experimental
Investigational medicinal product name	Tilpisertib
Investigational medicinal product code	
Other name	GS-4875
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

Arm title	Tilpisertib 100 mg (Blinded Treatment Phase)
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Arm description:

Tilpisertib 100 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive tilpisertib 100 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Arm type	Experimental
Investigational medicinal product name	Tilpisertib
Investigational medicinal product code	
Other name	GS-4875
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg administered once daily

Arm title	Placebo (Blinded Treatment Phase)
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Arm description:

Placebo tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive placebo tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Administered once daily	

Number of subjects in period 1	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)
Started	7	6	6
Completed	5	4	3
Not completed	2	2	3
Investigator's decision	-	1	-
Adverse event, non-fatal	-	-	1
Study terminated by sponsor	1	1	1
Disease worsening	-	-	1
Withdrew consent	1	-	-

Period 2

Period 2 title	Open-label Treatment Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tilpisertib 300 mg from Tilpisertib 300 mg (OLTP)

Arm description:

Participants who received tilpisertib 300 mg and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Arm type	Experimental
Investigational medicinal product name	Tilpisertib
Investigational medicinal product code	
Other name	GS-4875
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

Arm title	Tilpisertib 300 mg from Tilpisertib 100 mg (OLTP)
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Arm description:

Participants who received tilpisertib 100 mg and did not achieve clinical response per modified MCS at

Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Arm type	Experimental
Investigational medicinal product name	Tilpisertib
Investigational medicinal product code	
Other name	GS-4875
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

Arm title	Tilpisertib 300 mg from Placebo (OLTP)
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Arm description:

Participants who received placebo and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Arm type	Experimental
Investigational medicinal product name	Tilpisertib
Investigational medicinal product code	
Other name	GS-4875
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg administered once daily

Number of subjects in period 2^[1]	Tilpisertib 300 mg from Tilpisertib 300 mg (OLTP)	Tilpisertib 300 mg from Tilpisertib 100 mg (OLTP)	Tilpisertib 300 mg from Placebo (OLTP)
Started	4	3	3
Completed	1	1	0
Not completed	3	2	3
Investigator's decision	1	-	-
Disease worsening	1	-	1
Withdrew consent	1	1	1
Lost to follow-up	-	-	1
MCS response not achieved at open-label week 10	-	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Participants who completed the Blinded Treatment phase and did not achieve the clinical response per modified MCS at Week 10 entered in Open-label Treatment phase to receive tilpisertib 300 mg.

Baseline characteristics

Reporting groups

Reporting group title	Tilpisertib 300 mg (Blinded Treatment Phase)
Reporting group description:	
Tilpisertib 300 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per Modified Mayo Clinic score (MCS) at Week 10, continued to receive tilpisertib 300 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	
Reporting group title	Tilpisertib 100 mg (Blinded Treatment Phase)
Reporting group description:	
Tilpisertib 100 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive tilpisertib 100 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	
Reporting group title	Placebo (Blinded Treatment Phase)
Reporting group description:	
Placebo tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive placebo tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	

Reporting group values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)
Number of subjects	7	6	6
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	51	49	43
standard deviation	± 11.8	± 22.6	± 18.4
Gender categorical Units: Subjects			
Female	2	1	3
Male	5	5	3
Race			
Not Permitted means local regulators did not allow collection of race information.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	7	6	3
Other	0	0	1
Not Permitted	0	0	0
Ethnicity			
Not Permitted means local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	6	4	6
Hispanic or Latino	1	2	0
Not Permitted	0	0	0

Reporting group values	Total		
Number of subjects	19		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	6		
Male	13		
Race			
Not Permitted means local regulators did not allow collection of race information.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Black or African American	2		
Native Hawaiian or Other Pacific Islander	0		
White	16		
Other	1		
Not Permitted	0		
Ethnicity			
Not Permitted means local regulators did not allow collection of ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	16		
Hispanic or Latino	3		
Not Permitted	0		

End points

End points reporting groups

Reporting group title	Tilpisertib 300 mg (Blinded Treatment Phase)
Reporting group description: Tilpisertib 300 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per Modified Mayo Clinic score (MCS) at Week 10, continued to receive tilpisertib 300 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	
Reporting group title	Tilpisertib 100 mg (Blinded Treatment Phase)
Reporting group description: Tilpisertib 100 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive tilpisertib 100 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	
Reporting group title	Placebo (Blinded Treatment Phase)
Reporting group description: Placebo tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive placebo tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.	
Reporting group title	Tilpisertib 300 mg from Tilpisertib 300 mg (OLTP)
Reporting group description: Participants who received tilpisertib 300 mg and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).	
Reporting group title	Tilpisertib 300 mg from Tilpisertib 100 mg (OLTP)
Reporting group description: Participants who received tilpisertib 100 mg and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).	
Reporting group title	Tilpisertib 300 mg from Placebo (OLTP)
Reporting group description: Participants who received placebo and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).	

Primary: Percentage of Participants who Achieved Clinical Remission per Modified Mayo Clinic Score (MCS) at Week 10

End point title	Percentage of Participants who Achieved Clinical Remission per Modified Mayo Clinic Score (MCS) at Week 10 ^[1]
End point description: The modified MCS is a scoring system for assessment of ulcerative colitis (UC) activity and is composed of subscores from endoscopy (range: 0 to 3, where 0 = normal or inactive disease and 3 = severe disease [spontaneous bleeding, ulceration]), rectal bleeding (range: 0 to 3, where 0 = no blood seen and 3 = blood alone passes), stool frequency (range: 0 to 3, where 0 = normal number of stools and 3 = at least 5 or more stools more than normal), and physician's global assessment (PGA) (range: 0 to 3, where 0 = normal and 3 = severe disease). Total score for MCS ranges from 0 to 12 (sum of all subscores), with higher scores indicating higher disease activity. Clinical remission per modified MCS is defined as stool frequency subscore ≤ 1 and not greater than baseline, rectal bleeding subscore of 0, and endoscopic subscore ≤ 1 at Week 10. Full analysis set included all randomized participants who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Week 10	

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 formal statistical hypotheses were tested for the primary end point.

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: percentage of participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved Endoscopic Response at Week 10

End point title	Percentage of Participants who Achieved Endoscopic Response at Week 10
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End point description:

Endoscopic response was defined as an endoscopic subscore of ≤ 1 at Week 10. Endoscopic subscore is a part of the modified MCS which is a scoring system for assessment of UC activity. Endoscopic subscore range: 0 to 3, where 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern), 2 = moderate disease (marked erythema, lack of vascular pattern, friability, erosions), and 3 = severe disease (spontaneous bleeding, ulceration). Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Week 10

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: percentage of participants				
number (not applicable)	14.3	16.7	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved MCS Response at Week 10

End point title	Percentage of Participants who Achieved MCS Response at Week 10
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End point description:

The modified MCS is a scoring system for assessment of UC activity and is composed of subscores from endoscopy (range: 0 to 3, where 0 = normal or inactive disease and 3 = severe disease [spontaneous bleeding, ulceration]), rectal bleeding (range: 0 to 3, where 0 = no blood seen and 3 = blood alone passes), stool frequency (range: 0 to 3, where 0 = normal number of stools and 3 = at least 5 or more stools more than normal), and PGA (range: 0 to 3, where 0 = normal and 3 = severe disease). Total score for MCS ranges from 0 to 12 (sum of all subscores), with higher scores indicating higher disease activity. MCS response is defined as a decrease from baseline of ≥ 3 points and at least 30% in MCS, in addition to a ≥ 1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore ≤ 1 at Week 10. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Week 10

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: percentage of participants				
number (not applicable)	28.6	16.7	16.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved MCS Remission at Week 10

End point title	Percentage of Participants who Achieved MCS Remission at Week 10
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End point description:

The modified MCS is a scoring system for assessment of UC activity and is composed of subscores from endoscopy (range: 0 to 3, where 0 = normal or inactive disease and 3 = severe disease [spontaneous bleeding, ulceration]), rectal bleeding (range: 0 to 3, where 0 = no blood seen and 3 = blood alone passes), stool frequency (range: 0 to 3, where 0 = normal number of stools and 3 = at least 5 or more stools more than normal), and PGA (range: 0 to 3, where 0 = normal and 3 = severe disease). Total score for MCS ranges from 0 to 12 (sum of all subscores), with higher scores indicating higher disease activity. MCS remission is defined as a MCS score of ≤ 2 and no individual subscore > 1 at Week 10. Participants in the Full Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Week 10

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	6	6	
Units: percentage of participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved Histologic Remission Based Upon the Geboes Scale at Week 10

End point title	Percentage of Participants Who Achieved Histologic Remission Based Upon the Geboes Scale at Week 10
End point description:	
Geboes histologic remission was assessed by the Geboes histologic scores. Grade 0: Architectural changes (0.0=No abnormality to 0.3=Severe diffuse or multifocal abnormalities); Grade 1: Chronic inflammatory infiltrate (1.0=No increase to 1.3=Marked increase); Grade 2A: Eosinophils in lamina propria (2A.0=No increase to 2A.3=Marked increase); Grade 2B: Neutrophils in lamina propria (2B.0=No increase to 2B.3=Marked increase); Grade 3: Neutrophils in epithelium (3.0=None to 3.3=>50% crypts involved); Grade 4: Crypt destruction (4.0=none to 4.3=Unequivocal crypt destruction), and Grade 5: Erosions and ulcerations: (5.0=No erosion, ulceration or granulation to 5.4=Ulcer or granulation tissue). Histologic remission defined as having Grade 0 of ≤ 0.3 , Grade 1 of ≤ 1.1 , Grade 2a of $\leq 2A.3$, Grade 2b of 2B.0, Grade 3 of 3.0, Grade 4 of 4.0, and Grade 5 of 5.0. Score ranges from 0 to 5.4. Lower values indicate better outcome. Participants in the Full Analysis Set with at least 1 histological assessment were analyzed.	
End point type	Secondary
End point timeframe:	
Week 10	

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	4	
Units: percentage of participants				
number (not applicable)	16.7	16.7	25.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participants Who Experienced Treatment-
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End point description:

TEAEs for the Blinded Treatment phase are either defined as AEs with an onset date on or after the Blinded Treatment phase study drug start date and no later than 30 days after permanent discontinuation study drug if no Open-label Treatment phase study drug was taken, or any AEs with an onset date on or after the Blinded Treatment phase study drug start date and before the Open-label Treatment phase study drug start date if Open-label Treatment phase study drug was taken and/or any AEs leading to premature discontinuation of Blinded Treatment phase study drug. TEAEs for the Open-label Treatment phase are either defined as AEs with an onset date on or after the Open-label Treatment phase study drug start date and no later than 30 days after permanent discontinuation of the Open-label Treatment phase study drug and/or any AEs leading to premature discontinuation study drug. Safety Analysis Set included all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Blinded Treatment phase: First dose date up to 50.6 weeks plus 30 days; Open-label phase: First dose date up to 50.7 weeks plus 30 days

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	Tilpisertib 300 mg from Tilpisertib 300 mg (OLTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	6	4
Units: percentage of participants				
number (not applicable)	57.1	50.0	50.0	50.0

End point values	Tilpisertib 300 mg from Tilpisertib 100 mg (OLTP)	Tilpisertib 300 mg from Placebo (OLTP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: percentage of participants				
number (not applicable)	66.7	66.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced Laboratory Abnormalities

End point title	Percentage of Participants Who Experienced Laboratory Abnormalities
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End point description:

Treatment-emergent laboratory abnormalities for Blinded Treatment phase are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of Blinded Treatment phase study drug plus 30 days for participants who permanently discontinued study drug or before the first dose of Open-label Treatment phase study drug. For the Open-label Treatment phase, treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from Open-label baseline at any postbaseline time point, up to and including the date of last dose of Open-label Treatment phase study drug plus 30 days for participants

who permanently discontinued study drug. For maximum postbaseline toxicity grade, the most severe graded abnormality from all tests was counted for each patient. Grade 1:mild; Grade 2:moderate; Grade 3:severe; Grade 4:life-threatening. Participants in the Safety Analysis Set were analyzed.

End point type	Secondary
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End point timeframe:

Blinded Treatment phase: First dose date up to 50.6 weeks plus 30 days; Open-label phase: First dose date up to 50.7 weeks plus 30 days

End point values	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)	Tilpisertib 300 mg from Tilpisertib 300 mg (OLTP)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	6	4
Units: percentage of participants				
number (not applicable)				
Grade 1	42.9	66.7	16.7	25.0
Grade 2	28.6	33.3	50.0	25.0
Grade 3	14.3	0	0	25.0
Grade 4	0	0	0	0

End point values	Tilpisertib 300 mg from Tilpisertib 100 mg (OLTP)	Tilpisertib 300 mg from Placebo (OLTP)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: percentage of participants				
number (not applicable)				
Grade 1	33.3	66.7		
Grade 2	0	33.3		
Grade 3	66.7	0		
Grade 4	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: Blinded Treatment phase: First dose date up to 50.6 weeks plus 30 days; Open-label Treatment phase: First dose date up to 50.7 weeks plus 30 days; All-Cause Mortality: Enrollment up to Week 70.3

Adverse event reporting additional description:

Adverse Events: Safety Analysis Set included all participants who received at least one dose of study drug; All-Cause Mortality: All Randomized Analysis Set included all participants who were randomized in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Tilpisertib 300 mg (Blinded Treatment Phase)
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Reporting group description:

Tilpisertib 300 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive tilpisertib 300 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Reporting group title	Tilpisertib 100 mg (Blinded Treatment Phase)
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Reporting group description:

Tilpisertib 100 mg tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive tilpisertib 100 mg tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Reporting group title	Placebo (Blinded Treatment Phase)
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Reporting group description:

Placebo tablet orally once daily up to Week 10. Participants who achieved clinical response per modified MCS at Week 10, continued to receive placebo tablets orally once daily for a maximum of 50 weeks in the Blinded Treatment phase.

Reporting group title	Tilpisertib 300 mg From Tilpisertib 300 mg (OLTP)
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Reporting group description:

Participants who received tilpisertib 300 mg and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Reporting group title	Tilpisertib 300 mg From Tilpisertib 100 mg (OLTP)
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Reporting group description:

Participants who received tilpisertib 100 mg and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Reporting group title	Tilpisertib 300 mg From Placebo (OLTP)
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Reporting group description:

Participants who received placebo and did not achieve clinical response per modified MCS at Week 10 in the Blinded Treatment phase, received tilpisertib 300 mg tablets orally once daily for up to 50 weeks in the Open-label Treatment phase (OLTP).

Serious adverse events	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 6 (16.67%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Campylobacter infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tilpisertib 300 mg From Tilpisertib 300 mg (OLTP)	Tilpisertib 300 mg From Tilpisertib 100 mg (OLTP)	Tilpisertib 300 mg From Placebo (OLTP)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Proctalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (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			
Campylobacter infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (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	Tilpisertib 300 mg (Blinded Treatment Phase)	Tilpisertib 100 mg (Blinded Treatment Phase)	Placebo (Blinded Treatment Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	3 / 6 (50.00%)	2 / 6 (33.33%)
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	1 / 6 (16.67%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Ear and labyrinth disorders External ear inflammation subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Gastrointestinal disorders Colitis ulcerative subjects affected / exposed occurrences (all) Dyspepsia	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Haemorrhoids thrombosed subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2
Rash subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Rash erythematous subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Osteonecrosis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Infections and infestations			
Asymptomatic COVID-19 subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Cystitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hordeolum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Mastitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vitamin D deficiency			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Tilpisertib 300 mg From Tilpisertib 300 mg (OLTP)	Tilpisertib 300 mg From Tilpisertib 100 mg (OLTP)	Tilpisertib 300 mg From Placebo (OLTP)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Ear and labyrinth disorders External ear inflammation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Gastrointestinal disorders Colitis ulcerative subjects affected / exposed occurrences (all) Dyspepsia	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Haemorrhoids thrombosed subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Rash erythematous subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Osteonecrosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Infections and infestations			
Asymptomatic COVID-19 subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Cystitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mastitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2019	- Minor corrections and language revisions were made to provide clarity and consistency throughout the protocol - Updates to the Glossary of Abbreviations and Definition of Terms as needed per revisions to the protocol - Updated Study Design schema (Section 3) to reflect changes made to dosage in the protocol - Updated Study Procedures Table (Appendix 2 and Appendix 3) to reflect changes made to study visits assessments/procedures in the protocol as described in the summary of changes
19 June 2020	- Study GS-US-365-4237 is revised to become a blinded study - An unblinded sponsor data review has been added when 90 subjects reach Week 10 - Phase 1 study results from GS-US-365-4235 (Phase 1 CYP3A drug-drug interaction study) and GS-US-365-5588 (Phase 1 iohexol study) - Toxicology study results from TX-457-2018 (phototoxicity study in rats) and TX-365-2016 (39-week chronic toxicology study in monkeys) - Revisions to allowed concomitant medications based on the results of Phase 1 Study GS-US-365-4235

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 November 2020	Gilead made the decision to discontinue the development of tilpisertib since a new molecular entity was able to achieve greater target coverage. The decision was not due to any safety concerns.	-

Notes:

Limitations and caveats

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

Since only 19 participants were enrolled, none of the planned statistical analyses were performed. During the COVID-19 pandemic, there were changes to protocol visits and procedures where necessary to mitigate the impact of the pandemic to the study.

Notes: