



Clinical trial results:

An adaptive Phase 2 randomized double-blind, placebo-controlled multi-center study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (LOUISse)

Summary

EudraCT number	2018-004387-54
Trial protocol	DE HU GB ES BE DK BG
Global end of trial date	23 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	CLOU064E12201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04035668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	23 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to characterize the dose-response relationship of remibrutinib based on change from baseline in EULAR Sjögren's syndrome Disease Activity Index (ESSDAI) at Week 24*.

*The change from baseline in ESSDAI at Week 24 of Part 1 was analyzed and reported. The dose-response relationship was not evaluated as it was planned as per the statistical analysis plan for Part 2 which was not conducted.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	China: 7
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	73
EEA total number of subjects	33

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)	58
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 26 investigative sites in 12 countries.

Pre-assignment

Screening details:

The screening period of up to 6 weeks began after the subject had provided written informed consent. Eligible subjects were randomized in a 1:1:1 ratio to one of the 3 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Remibrutinib 100 mg bid
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Arm description:

Remibrutinib 100 mg twice daily (bid)

Arm type	Experimental
Investigational medicinal product name	Remibrutinib
Investigational medicinal product code	LOU064
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Remibrutinib 100 mg was administered orally as two 50 mg hard gelatin capsules. Patients in the remibrutinib 100 mg twice daily (bid) dose group took 2 capsules of active medication in the morning and 2 capsules of active medication in the evening.

Arm title	Remibrutinib 100 mg qd
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Arm description:

Remibrutinib 100 mg once daily (qd)

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

Dosage and administration details:

Patients took 2 capsules of active medication in the morning and 2 capsules of the placebo in the evening.

Investigational medicinal product name	Remibrutinib
Investigational medicinal product code	LOU064
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Remibrutinib 100 mg was administered orally as two 50 mg hard gelatin capsules. Patients in the remibrutinib 100 mg once daily (qd) dose group took 2 capsules of active medication in the morning and

2 capsules of the placebo in the evening.

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

Dosage and administration details:

Placebo was administered orally as two hard gelatin capsules. Patients in the placebo dose group took 2 capsules of placebo in the morning and 2 capsules of placebo in the evening.

Number of subjects in period 1	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo
Started	24	25	24
Completed	17	17	21
Not completed	7	8	3
Physician decision	2	1	1
Subject Decision	2	2	-
Adverse event	3	4	2
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Remibrutinib 100 mg bid
Reporting group description: Remibrutinib 100 mg twice daily (bid)	
Reporting group title	Remibrutinib 100 mg qd
Reporting group description: Remibrutinib 100 mg once daily (qd)	
Reporting group title	Placebo
Reporting group description: Placebo group	

Reporting group values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo
Number of subjects	24	25	24
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)	19	21	18
From 65-84 years	5	4	6
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.5	54.8	51.0
standard deviation	± 15.21	± 10.51	± 13.94
Sex: Female, Male Units: participants			
Female	24	24	23
Male	0	1	1
Race/Ethnicity, Customized Units: Subjects			
Asian	7	7	7
White	17	17	16
Unknown	0	1	0
Black or African American	0	0	1

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	58		
From 65-84 years	15		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	71		
Male	2		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	21		
White	50		
Unknown	1		
Black or African American	1		

Subject analysis sets

Subject analysis set title	Any remibrutinib
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients in any of the two remibrutinib treatment groups	

Reporting group values	Any remibrutinib		
Number of subjects	49		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	40		
From 65-84 years	9		
85 years and over	0		
Age Continuous			
Units: years			
arithmetic mean	52.2		
standard deviation	± 13.6		

Sex: Female, Male Units: participants			
Female	48		
Male	1		
Race/Ethnicity, Customized Units: Subjects			
Asian	14		
White	34		
Unknown	1		
Black or African American	0		

End points

End points reporting groups

Reporting group title	Remibrutinib 100 mg bid
Reporting group description:	
Remibrutinib 100 mg twice daily (bid)	
Reporting group title	Remibrutinib 100 mg qd
Reporting group description:	
Remibrutinib 100 mg once daily (qd)	
Reporting group title	Placebo
Reporting group description:	
Placebo group	
Subject analysis set title	Any remibrutinib
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients in any of the two remibrutinib treatment groups	

Primary: Change from baseline in EULAR Sjögren's syndrome Disease Activity Index (ESSDAI) total score at Week 24

End point title	Change from baseline in EULAR Sjögren's syndrome Disease Activity Index (ESSDAI) total score at Week 24
End point description:	
<p>ESSDAI is a validated disease outcome measure for Sjögren's Syndrome. The instrument contains 12 organ-specific domains contributing to disease activity: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological and biological. For each domain, features of disease activity were scored according to their severity. These scores were summed across the 12 domains in a weighted manner to provide the total score. ESSDAI total score ranges from 0 to 123 with higher values indicating more disease activity. A negative change from baseline indicates improvement.</p> <p>The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.</p> <p>A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in ESSDAI for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table</p>	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	24	24	48
Units: score on scale				
least squares mean (standard error)	-3.70 (± 0.80)	-4.70 (± 0.78)	-1.34 (± 0.74)	-4.20 (± 0.56)

Statistical analyses

Statistical analysis title	Week 24 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[1]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.71
upper limit	-1.01

Notes:

[1] - one-sided p-value

Statistical analysis title	Week 24 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg bid v Remibrutinib 100 mg qd
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	1.25

Secondary: Change from baseline in ESSDAI total score over time

End point title	Change from baseline in ESSDAI total score over time
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End point description:

ESSDAI is a validated disease outcome measure for Sjögren's Syndrome. The instrument contains 12 organ-specific domains contributing to disease activity: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological and biological. For each domain, features of disease activity were scored according to their severity. These scores were summed across the 12 domains in a weighted manner to provide the total score. ESSDAI total score ranges from 0 to 123 with higher values indicating more disease activity. A negative change from baseline indicates improvement.

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in ESSDAI for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16 and Week 20

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	24	24	48
Units: score on scale				
least squares mean (standard error)				
Week 2	-1.05 (± 0.52)	-1.68 (± 0.52)	-0.37 (± 0.55)	-1.37 (± 0.37)
Week 4	-2.54 (± 0.62)	-2.57 (± 0.60)	-0.79 (± 0.61)	-2.55 (± 0.43)
Week 8	-2.93 (± 0.71)	-2.74 (± 0.72)	-2.36 (± 0.69)	-2.83 (± 0.51)
Week 12	-2.56 (± 0.75)	-3.66 (± 0.74)	-1.92 (± 0.73)	-3.11 (± 0.53)
Week 16	-2.57 (± 0.74)	-4.02 (± 0.71)	-2.16 (± 0.69)	-3.29 (± 0.51)
Week 20	-3.26 (± 0.75)	-4.40 (± 0.73)	-1.84 (± 0.69)	-3.83 (± 0.52)

Statistical analyses

Statistical analysis title	Week 2 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065 ^[2]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	0.3

Notes:

[2] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 ^[3]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	-0.29

Notes:

[3] - one-sided p-value

Statistical analysis title	Week 16 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094 ^[4]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	0.57

Notes:

[4] - one-sided p-value

Statistical analysis title	Week 12 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.093 ^[5]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	0.59

Notes:

[5] - one-sided p-value

Statistical analysis title	Week 8 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.289 ^[6]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	1.22

Notes:

[6] - one-sided p-value

Statistical analysis title	Week 20 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 ^[7]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.71
upper limit	-0.28

Notes:

[7] - one-sided p-value

Statistical analysis title	Week 2 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	0.84

Statistical analysis title	Week 4 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.75
upper limit	1.69

Statistical analysis title	Week 8 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.83
upper limit	2.21

Statistical analysis title	Week 12 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.01

Statistical analysis title	Week 16 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	0.6

Statistical analysis title	Week 20 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.22
upper limit	0.95

Secondary: Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) total score over time

End point title	Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) total score over time
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End point description:

ESSPRI is an established disease outcome measure for Sjögren's Syndrome. It consists of three domains of dryness, pain, and fatigue. The patient can assess the severity of symptoms they experience on a single 0-10 numerical scale for each of the three domains. The ESSPRI score is defined as the mean of scores from the three scales: (dryness + pain + fatigue) / 3. ESSPRI total score ranges from 0 to 10 with higher values indicating more disease symptoms. A negative change from baseline indicates improvement.

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in ESSPRI for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	24	24	48
Units: score on scale				
least squares mean (standard error)				
Week 2	0.18 (± 0.26)	-0.44 (± 0.26)	-0.09 (± 0.27)	-0.13 (± 0.18)
Week 4	-0.14 (± 0.30)	-0.72 (± 0.30)	-0.35 (± 0.30)	-0.43 (± 0.21)
Week 8	-0.38 (± 0.31)	-0.83 (± 0.31)	-0.57 (± 0.29)	-0.60 (± 0.22)
Week 12	-0.32 (± 0.31)	-0.88 (± 0.31)	-0.66 (± 0.29)	-0.60 (± 0.22)
Week 16	-0.39 (± 0.37)	-0.77 (± 0.36)	-0.71 (± 0.34)	-0.58 (± 0.26)
Week 20	-0.74 (± 0.39)	-0.92 (± 0.38)	-0.92 (± 0.36)	-0.83 (± 0.27)

Week 24	-0.76 (\pm 0.35)	-1.17 (\pm 0.34)	-1.13 (\pm 0.31)	-0.96 (\pm 0.24)
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Statistical analyses

Statistical analysis title	Week 2 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 ^[8]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.62

Notes:

[8] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.418 ^[9]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.66

Notes:

[9] - one-sided p-value

Statistical analysis title	Week 8 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.466 ^[10]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	0.7

Notes:

[10] - one-sided p-value

Statistical analysis title	Week 12 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56 ^[11]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.79

Notes:

[11] - one-sided p-value

Statistical analysis title	Week 16 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616 ^[12]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.99

Notes:

[12] - one-sided p-value

Statistical analysis title	Week 20 Remibrutinib vs Placebo
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Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.581 ^[13]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	0.99

Notes:

[13] - one-sided p-value

Statistical analysis title	Week 24 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.663 ^[14]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.96

Notes:

[14] - one-sided p-value

Statistical analysis title	Week 2 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	0.11

Statistical analysis title	Week 4 Remibrutinib qd vs bid
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Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	0.26

Statistical analysis title	Week 8 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	0.42

Statistical analysis title	Week 12 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	0.31

Statistical analysis title	Week 16 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	0.65

Statistical analysis title	Week 20 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.39
upper limit	0.65

Statistical analysis title	Week 24 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	0.57

Secondary: Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) total score over time

End point title	Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) total score over time
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End point description:

FACIT-F v4 is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue was measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). FACIT-F total score ranges from 0 to 52 with higher values indicating higher quality of life (less fatigue). A positive change from baseline is a favorable outcome.

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in FACIT-F for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table.

End point type	Secondary
End point timeframe:	
Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24	

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	23	47
Units: score on scale				
least squares mean (standard error)				
Week 2	-0.51 (± 1.35)	1.80 (± 1.32)	3.37 (± 1.43)	0.64 (± 0.95)
Week 4	3.97 (± 1.57)	4.83 (± 1.50)	3.51 (± 1.58)	4.40 (± 1.09)
Week 8	3.79 (± 1.66)	4.00 (± 1.64)	5.26 (± 1.60)	3.90 (± 1.17)
Week 12	4.25 (± 1.86)	4.88 (± 1.80)	7.30 (± 1.77)	4.56 (± 1.30)
Week 16	3.29 (± 2.08)	4.40 (± 1.97)	7.73 (± 1.98)	3.84 (± 1.44)
Week 20	4.32 (± 2.30)	10.01 (± 2.20)	5.77 (± 2.17)	7.16 (± 1.60)
Week 24	4.64 (± 2.55)	8.17 (± 2.45)	7.45 (± 2.32)	6.40 (± 1.77)

Statistical analyses

Statistical analysis title	Week 2 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 ^[15]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.18
upper limit	0.73

Notes:

[15] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib vs Placebo
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Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.322 ^[16]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.95
upper limit	4.74

Notes:

[16] - one-sided p-value

Statistical analysis title	Week 8 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.753 ^[17]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.32
upper limit	2.59

Notes:

[17] - one-sided p-value

Statistical analysis title	Week 12 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.891 ^[18]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.13
upper limit	1.66

Notes:

[18] - one-sided p-value

Statistical analysis title	Week 16 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.941 ^[19]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.77
upper limit	1.01

Notes:

[19] - one-sided p-value

Statistical analysis title	Week 20 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304 ^[20]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	6.79

Notes:

[20] - one-sided p-value

Statistical analysis title	Week 24 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64 ^[21]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.89
upper limit	4.79

Notes:

[21] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	5.18

Statistical analysis title	Week 2 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.44
upper limit	6.07

Statistical analysis title	Week 8 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.43
upper limit	4.83

Statistical analysis title	Week 12 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.53
upper limit	5.78

Statistical analysis title	Week 20 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	5.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	12.04

Statistical analysis title	Week 16 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6
upper limit	6.82

Statistical analysis title	Week 24 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	3.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.53
upper limit	10.59

Secondary: Change from baseline in EuroQual 5 dimensions (EQ-5D) VAS score over time

End point title	Change from baseline in EuroQual 5 dimensions (EQ-5D) VAS score over time
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End point description:

EQ-5D is a standardized instrument that measures the health-related quality of life. The EQ-5D consists of a descriptive system and a visual analog scale (VAS). The EQ-5D VAS records the patient's self-rated health on a vertical visual analogue scale with 0 representing 'Worst imaginable Health State' and 100 'Best imaginable Health State'. A positive change from baseline is a favorable outcome.

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in EQ-5D VAS score for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table.

End point type	Secondary
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End point timeframe:

Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	23	24	23	47
Units: score on scale				
least squares mean (standard error)				
Week 2	-2.86 (± 3.16)	-3.05 (± 3.11)	-3.02 (± 3.28)	-2.95 (± 2.22)
Week 4	-0.03 (± 2.86)	-1.74 (± 2.71)	2.99 (± 2.87)	-0.88 (± 1.97)
Week 8	1.76 (± 3.20)	1.46 (± 3.20)	3.44 (± 3.04)	1.61 (± 2.26)
Week 12	1.58 (± 2.82)	-2.36 (± 2.71)	4.00 (± 2.64)	-0.39 (± 1.95)
Week 16	4.27 (± 3.54)	-0.44 (± 3.27)	1.79 (± 3.28)	1.92 (± 2.41)
Week 20	5.37 (± 3.33)	-0.91 (± 3.15)	5.29 (± 3.01)	2.23 (± 2.29)
Week 24	5.73 (± 3.65)	1.81 (± 3.47)	2.07 (± 3.22)	3.77 (± 2.52)

Statistical analyses

Statistical analysis title	Week 2 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.494 ^[22]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.84
upper limit	7.96

Notes:

[22] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.866 ^[23]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.81
upper limit	3.06

Notes:

[23] - one-sided p-value

Statistical analysis title	Week 8 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684 ^[24]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.37
upper limit	5.73

Notes:

[24] - one-sided p-value

Statistical analysis title	Week 12 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.908 ^[25]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-4.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.93
upper limit	2.14

Notes:

[25] - one-sided p-value

Statistical analysis title	Week 16 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.487 ^[26]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8
upper limit	8.26

Notes:

[26] - one-sided p-value

Statistical analysis title	Week 20 Remibrutinib vs Placebo
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Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 ^[27]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.61
upper limit	4.49

Notes:

[27] - one-sided p-value

Statistical analysis title	Week 24 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34 ^[28]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.48
upper limit	9.88

Notes:

[28] - one-sided p-value

Statistical analysis title	Week 8 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.34
upper limit	8.74

Statistical analysis title	Week 4 Remibrutinib qd vs bid
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Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.59
upper limit	6.17

Statistical analysis title	Week 2 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.06
upper limit	8.68

Statistical analysis title	Week 20 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-6.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.44
upper limit	2.87

Statistical analysis title	Week 16 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-4.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.34
upper limit	4.93

Statistical analysis title	Week 12 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.74
upper limit	3.86

Statistical analysis title	Week 24 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-3.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.01
upper limit	6.16

Secondary: Change from baseline in Physician Global Assessment Scale (PhGA) score over time

End point title	Change from baseline in Physician Global Assessment Scale (PhGA) score over time
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End point description:

The physician's global assessment scale was used for the Investigator to rate the disease activity of their patient using 100 mm visual analog scale (VAS) ranging from "no disease activity" (0) to "maximal disease activity" (100). A negative change from baseline indicates improvement.

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

A mixed effect model for repeated measurements (MMRM) was fitted to the changes from baseline in PhGA score for all post-baseline time points up to Week 24. Values estimated from the model are presented in this table.

End point type	Secondary
End point timeframe:	
Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24	

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Any remibrutinib
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	24	24	24	48
Units: score on scale				
least squares mean (standard error)				
Week 2	-4.02 (± 2.85)	-4.21 (± 2.90)	-4.82 (± 3.10)	-4.12 (± 2.04)
Week 4	-8.93 (± 2.96)	-9.58 (± 2.89)	-7.28 (± 2.95)	-9.26 (± 2.08)
Week 8	-13.78 (± 3.28)	-13.68 (± 3.39)	-13.23 (± 3.16)	-13.73 (± 2.37)
Week 12	-9.45 (± 3.68)	-13.85 (± 3.63)	-17.67 (± 3.52)	-11.65 (± 2.60)
Week 16	-7.25 (± 3.74)	-19.37 (± 3.61)	-15.90 (± 3.51)	-13.31 (± 2.61)
Week 20	-17.31 (± 3.48)	-23.56 (± 3.43)	-17.57 (± 3.20)	-20.43 (± 2.45)
Week 24	-13.15 (± 3.95)	-21.25 (± 3.88)	-20.15 (± 3.54)	-17.20 (± 2.78)

Statistical analyses

Statistical analysis title	Week 8 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45 ^[29]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	7.41

Notes:

[29] - one-sided p-value

Statistical analysis title	Week 4 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.294 ^[30]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-1.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.22
upper limit	5.27

Notes:

[30] - one-sided p-value

Statistical analysis title	Week 2 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575 ^[31]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.75
upper limit	8.16

Notes:

[31] - one-sided p-value

Statistical analysis title	Week 20 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241 ^[32]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-2.86

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.96
upper limit	5.24

Notes:

[32] - one-sided p-value

Statistical analysis title	Week 16 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.722 ^[33]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.16
upper limit	11.34

Notes:

[33] - one-sided p-value

Statistical analysis title	Week 12 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913 ^[34]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	6.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	14.78

Notes:

[34] - one-sided p-value

Statistical analysis title	Week 24 Remibrutinib vs Placebo
Comparison groups	Placebo v Any remibrutinib

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.742 ^[35]
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.09
upper limit	11.99

Notes:

[35] - one-sided p-value

Statistical analysis title	Week 2 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.28
upper limit	7.91

Statistical analysis title	Week 4 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.87
upper limit	7.58

Statistical analysis title	Week 8 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.28
upper limit	9.48

Statistical analysis title	Week 12 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.71
upper limit	5.9

Statistical analysis title	Week 16 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.47
upper limit	-1.77

Statistical analysis title	Week 20 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-6.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	3.5

Statistical analysis title	Week 24 Remibrutinib qd vs bid
Comparison groups	Remibrutinib 100 mg qd v Remibrutinib 100 mg bid
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
Method	MMRM
Parameter estimate	Mean difference (final values)
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.16
upper limit	2.96

Secondary: Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs
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End point description:

Number of participants with TEAEs and serious TEAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as TEAEs. TEAEs are defined as adverse events that started after the first dose of study medications or adverse events present prior to start of double-blind treatment but increased in severity.

The number of participants in each category is reported in the table.

End point type	Secondary
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End point timeframe:

From first dose of study treatment up 30 days after last dose (Week 29)

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	24	
Units: participants				
TEAE	22	21	20	
Study drug-related TEAE	10	8	9	
Serious TEAE	1	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed blood concentration (C_{max}) of remibrutinib at Week 4

End point title	Maximum observed blood concentration (C _{max}) of remibrutinib at Week 4 ^[36]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. C_{max} is defined as the maximum (peak) observed blood concentration following a dose.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: ng/mL				
arithmetic mean (standard deviation)	183 (± 82.5)	225 (± 154)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed blood concentration (C_{max}) of remibrutinib at Week 24

End point title	Maximum observed blood concentration (C _{max}) of remibrutinib at Week 24 ^[37]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL.

Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. Cmax is defined as the maximum (peak) observed blood concentration following a dose.

End point type	Secondary
End point timeframe:	
pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24	

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: ng/mL				
arithmetic mean (standard deviation)	224 (± 202)	169 (± 77.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 4

End point title	Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 4 ^[38]
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End point description:

Remibrutinib was determined in whole blood by a validated LC-MS/MS method with a LLOQ of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. Tmax is defined as the time to reach maximum (peak) blood concentration following a dose.

End point type	Secondary
End point timeframe:	
pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4	

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: hours				
median (full range (min-max))	1.00 (0.500 to 3.00)	1.00 (0.500 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 24

End point title	Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 24 ^[39]
-----------------	--

End point description:

Remibrutinib was determined in whole blood by a validated LC-MS/MS method with a LLOQ of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. Tmax is defined as the time to reach maximum (peak) blood concentration following a dose.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: hours				
median (full range (min-max))	1.00 (0.500 to 3.00)	1.00 (0.500 to 3.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 4

End point title	Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 4 ^[40]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. AUCtau is defined as the area under the blood concentration-time curve calculated/extrapolated to the end of a dosing interval (tau) at steady-state. Tau was 24 hours for the qd dosing group and 12 hours for the bid dosing group. For the calculation of AUCtau, the pre-dose concentrations at Week 4 and Week 24 were duplicated as 24 hours and 12 hours concentrations for the qd and bid groups, respectively. The linear trapezoidal method was used for AUCtau calculation.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	8		
Units: h*ng/mL				
arithmetic mean (standard deviation)	569 (± 311)	1020 (± 700)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 24

End point title	Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 24 ^[41]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. AUCtau is defined as the area under the blood concentration-time curve calculated/extrapolated to the end of a dosing interval (tau) at steady-state. Tau was 24 hours for the qd dosing group and 12 hours for the bid dosing group. For the calculation of AUCtau, the pre-dose concentrations at Week 4 and Week 24 were duplicated as 24 hours and 12 hours concentrations for the qd and bid groups, respectively. The linear trapezoidal method was used for AUCtau calculation.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: h*ng/mL				
arithmetic mean (standard deviation)	670 (± 380)	636 (± 306)		

Statistical analyses

Secondary: Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 4

End point title	Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 4 ^[42]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. AUC0-4h is defined as the area under the blood concentration-time curve from time zero to 4 hours post-dose, which was the last sampling time. The linear trapezoidal method was used for AUC0-4h calculation.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: h*ng/mL				
arithmetic mean (standard deviation)	351 (± 169)	393 (± 207)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 24

End point title	Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 24 ^[43]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. AUC0-4h is defined as the area under the blood concentration-time curve from time zero to 4 hours post-dose, which was the last sampling time. The linear trapezoidal method was used for AUC0-4h calculation.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	10		
Units: h*ng/mL				
arithmetic mean (standard deviation)	420 (± 259)	317 (± 144)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life (T1/2) of remibrutinib at Week 4

End point title	Elimination half-life (T1/2) of remibrutinib at Week 4 ^[44]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. T1/2 is defined as the time taken for the blood concentration, as well as the amount of the drug in the body, to fall by one-half.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: hours				
arithmetic mean (standard deviation)	3.08 (± 0.998)	3.86 (± 2.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination half-life (T1/2) of remibrutinib at Week 24

End point title	Elimination half-life (T1/2) of remibrutinib at Week 24 ^[45]
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End point description:

Remibrutinib was determined in whole blood by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL. Pharmacokinetic (PK) parameters were calculated based on remibrutinib blood concentrations by using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (version 8 or higher). Concentrations below the LLOQ were treated as zero. T1/2 is defined as the time taken for the blood concentration, as well as the amount of the drug in the body, to fall by one-half.

End point type	Secondary
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End point timeframe:

pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK parameters were only applicable to remibrutinib groups.

End point values	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: hours				
arithmetic mean (standard deviation)	3.15 (\pm 0.907)	3.88 (\pm 1.95)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up 30 days after last dose (Week 29)

Adverse event reporting additional description:

Any sign or symptom that occurs from first dose of study treatment up to 30 days after last dose.

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	Remibrutinib 100 mg bid
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Reporting group description:

Remibrutinib 100 mg twice daily (bid)

Reporting group title	Remibrutinib 100 mg qd
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Reporting group description:

Remibrutinib 100 mg once daily (qd)

Reporting group title	Total
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Reporting group description:

All participants

Reporting group title	Placebo
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Reporting group description:

Placebo group

Reporting group title	Any remibrutinib
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Reporting group description:

Patients in any of the two remibrutinib treatment groups

Serious adverse events	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	1 / 25 (4.00%)	3 / 73 (4.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 25 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 24 (0.00%)	1 / 25 (4.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	1 / 73 (1.37%)
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	Placebo	Any remibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	2 / 49 (4.08%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 24 (0.00%)	1 / 49 (2.04%)	
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 / 24 (4.17%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 24 (62.50%)	12 / 25 (48.00%)	44 / 73 (60.27%)
Investigations			
Blood immunoglobulin G increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	2 / 24 (8.33%)	1 / 25 (4.00%)	3 / 73 (4.11%)
occurrences (all)	2	1	3

Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 25 (0.00%) 0	2 / 73 (2.74%) 2
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	3 / 25 (12.00%) 3	9 / 73 (12.33%) 10
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1	0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 1 / 25 (4.00%) 3	3 / 73 (4.11%) 3 3 / 73 (4.11%) 3 4 / 73 (5.48%) 6
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0 3 / 24 (12.50%) 3	2 / 25 (8.00%) 2 0 / 25 (0.00%) 0	3 / 73 (4.11%) 3 5 / 73 (6.85%) 6
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea	0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 2 / 24 (8.33%) 2	0 / 25 (0.00%) 0 2 / 25 (8.00%) 2 0 / 25 (0.00%) 0	2 / 73 (2.74%) 3 4 / 73 (5.48%) 4 3 / 73 (4.11%) 3

subjects affected / exposed occurrences (all)	4 / 24 (16.67%) 4	1 / 25 (4.00%) 1	7 / 73 (9.59%) 7
Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 25 (0.00%) 0	2 / 73 (2.74%) 2
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 25 (8.00%) 2	4 / 73 (5.48%) 4
Arthralgia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	2 / 25 (8.00%) 4	4 / 73 (5.48%) 7
Myalgia subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 25 (4.00%) 1	3 / 73 (4.11%) 3
Sjogren's syndrome subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	0 / 25 (0.00%) 0	2 / 73 (2.74%) 2
Muscle spasms subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	2 / 25 (8.00%) 2	2 / 73 (2.74%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	1 / 25 (4.00%) 1	6 / 73 (8.22%) 8
Sinusitis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	0 / 25 (0.00%) 0	2 / 73 (2.74%) 2
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3	0 / 25 (0.00%) 0	5 / 73 (6.85%) 6
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 25 (4.00%) 1	4 / 73 (5.48%) 4
Metabolism and nutrition disorders			

Hypokalaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 25 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	3

Non-serious adverse events	Placebo	Any remibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 24 (70.83%)	27 / 49 (55.10%)	
Investigations			
Blood immunoglobulin G increased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	0 / 24 (0.00%)	3 / 49 (6.12%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 24 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 24 (20.83%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Lymphopenia			
subjects affected / exposed	3 / 24 (12.50%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Fatigue			

subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3	3 / 49 (6.12%) 3	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 24 (8.33%)	0 / 49 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	1 / 24 (4.17%)	3 / 49 (6.12%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)	2 / 49 (4.08%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	2 / 24 (8.33%)	5 / 49 (10.20%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 24 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 24 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	2	2	
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)	3 / 49 (6.12%)	
occurrences (all)	2	5	
Myalgia			
subjects affected / exposed	2 / 24 (8.33%)	1 / 49 (2.04%)	
occurrences (all)	2	1	
Sjogren's syndrome			
subjects affected / exposed	0 / 24 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	0 / 24 (0.00%)	2 / 49 (4.08%)	
occurrences (all)	0	2	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	3 / 24 (12.50%)	3 / 49 (6.12%)	
occurrences (all)	4	4	
Sinusitis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 49 (0.00%)	
occurrences (all)	2	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 24 (8.33%)	3 / 49 (6.12%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	2 / 24 (8.33%)	2 / 49 (4.08%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 49 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2019	The reason for this amendment was to respond and comply with change requests received from a regulatory authority following the first submission of the original protocol. It included a clarification of exclusion criterion number 20 on male sterilization, the deletion of the term "guardian" and a clarification of the study stopping rules.
08 June 2020	<p>This amendment primarily aimed to align the eligibility criterion for resting heart rate (exclusion criterion #11) with a normal resting heart rate of Sjögren's Syndrome (SjS) patients and with that of the parallel LOU064 protocols. Lowering the minimum required resting heart rate to 50 bpm (from 60 bpm) does not impact patient safety as LOU064 does not have a negative chronotropic effect. The reference point for stop of previous treatments (exclusion criterion #2) and dose adjustments for concomitant treatments (exclusion criterion #4) was changed from screening to baseline, to reflect the starting point of the additional experimental study treatment.</p> <p>Chloroquine in a dose up to 250 mg/day was added as an alternative allowed concomitant therapy to hydroxychloroquine (exclusion criterion #6). These treatments cover the same pharmacological principles but have different availability in different countries.</p> <p>Other changes were made to clarify inconsistencies and to make minor corrections.</p> <p>The introduced changes did not significantly impact patient safety, study population, trial conduct, or scientific value of the trial.</p>
05 November 2020	<p>The main purpose of this protocol amendment was to extend unblinding of interim analysis 1 and 2 (Part 1 data) to other sponsor staff. This did allow the clinical team to share unblinded results with sponsor decision boards as required for appropriate decision making on the study and on the project. Investigators and study patients will remain blinded throughout the study. Part 2 of the study will remain blinded until the final analysis for the sponsor too.</p> <p>Consequently, to ensure that the unblinding of Part 1 did not bias the assessment of the primary objective of the study, only Part 2 data will be used for the primary analysis of the entire study.</p> <p>The replacement policy was updated to allow for over recruitment of Part 1 patients in case of a higher than expected early discontinuation rate.</p> <p>Regarding the coronavirus disease 2019 (COVID-19) pandemic, the situation and benefit-risk assessment was carefully considered for this study. Based on these considerations, it was not considered that the COVID-19 pandemic changes the overall risk-benefit assessment for this study and therefore no changes regarding this topic were included in this amendment. However, in order to reduce study patients from potential viral exposure, some study procedures including hospital visits may need to be modified which could lead to protocol deviations.</p> <p>Other changes were made to clarify inconsistencies and to make minor corrections.</p>

12 February 2021	<p>The main purpose of this protocol amendment was a formulation switch from hard gelatin capsules to film-coated tablets to be effective only for Part 2 of the study. The patients in Part 2 were to be provided film-coated tablets, however, patients in Part 1 did continue receiving hard gelatin capsules. Film-coated tablets were to be introduced in Part 2 of the study as this formulation is the proposed market formulation. A relative bioavailability study (CLOU064X2105) has been conducted to compare the exposure of both formulations. Initial results indicated that C_{max} and AUC values were in line with results from the first in human study (CLOU064X2101) given the high variability in the PK of LOU064 seen in all clinical trials. Despite the fact that C_{max} and AUC were slightly lower for the film-coated tablets when compared to the hard gelatin capsules there is no change in the benefit-risk, the safety or drug-drug interaction profile and no requirement to adapt the dose. The inclusion of the film-coated tablets in Part 2 was to support the seamless switch to the final market image to be used in all Phase III trials. The patient replacement policy was updated to allow for patients over recruitment in Part 2 in case of higher than expected early discontinuation rate not due to adverse drug reactions or adverse events.</p>
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported