



Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Remibrutinib

Trial Indication(s)

Sjögren's Syndrome

Protocol Number

CLOU064E12201

Protocol Title

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)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: July 2019 (Actual)

Primary Completion Date: November 2021 (Actual)

Study Completion Date: November 2021 (Actual)

Reason for Termination (If applicable)

Following favorable efficacy and safety results of interim analysis 2 at the end of Part 1, the sponsor decided to assess any future development of remibrutinib in Sjögren's Syndrome within separate clinical studies. Therefore, this study was terminated early on 26-Apr-2022 and did not continue with Part 2 of the study. The dose-response evaluation of the dosing regimen (once daily or twice daily) planned for Part 2 of the study was not conducted. There were no safety reasons associated with the decision for the early termination of this study.

Study Design/Methodology

This study was planned as an adaptive Phase 2 randomized, double-blind, placebo-controlled, multi-center, integrated dose-ranging study to evaluate the safety and efficacy of multiple remibrutinib doses in patients with moderate to severe Sjögren's Syndrome (SjS).

Of the initially planned two parts, only Part 1 of the study was conducted. In Part 1, the highest expected biologically active single dose of remibrutinib (100 mg) was tested in two different dosing regimens, a once daily dose (qd) or twice daily dose (bid), and compared to the placebo group. Each patient in Part 1 of the study underwent a screening period of up to 6 weeks, a treatment period of 24 weeks, and a follow-up period of 30 days post-treatment before the End of Study (EOS) visit. The total duration for each patient in the study, including Screening, was up to 35 weeks. For the treatment period, patients were randomized in a 1:1:1 ratio to one of the 3 treatment groups: remibrutinib 100 mg bid, remibrutinib 100 mg qd and placebo.

Centers

26 centers in 12 countries/regions: Germany(1), Hungary(1), Australia(3), Switzerland(2), Spain(5), Bulgaria(1), Denmark(1), Belgium(1), Taiwan(4), China(3), United Kingdom(3), United States(1)

Objectives:

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*.

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*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.

The secondary objectives of the trial were:

- To evaluate the efficacy of remibrutinib compared to placebo with respect to change from baseline on patient- and physician-reported outcomes over time
- To evaluate the dose-response profile of remibrutinib based on change in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) at Week 24
- To evaluate the efficacy of remibrutinib compared to placebo with respect to change from baseline in ESSDAI over time
- To evaluate the safety and tolerability of remibrutinib
- To assess PK parameters of remibrutinib

Based on the primary and secondary objectives, the following endpoints were assessed:

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

	<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 the table.</p>
<p>Secondary: Change from baseline in ESSDAI total score over time</p>	<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 the table.</p>
<p>Secondary: Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) total score over time</p>	<p>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.</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 ESSPRI for all post-baseline time points up to Week 24. Values estimated from the model are presented in the table.</p>
<p>Secondary: Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) total score over time</p>	<p>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.</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 FACIT-F for all post-baseline time points up to Week 24. Values estimated from the model are presented in the table.</p>
<p>Secondary: Change from baseline in EuroQual 5 dimensions (EQ-5D) VAS score over time</p>	<p>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.</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 EQ-5D VAS score for all post-baseline time points up to Week 24. Values estimated from the model are presented in the table.</p>

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<p>Secondary: Change from baseline in Physician Global Assessment Scale (PhGA) score over time</p>	<p>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.</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 PhGA score for all post-baseline time points up to Week 24. Values estimated from the model are presented in the table.</p>
<p>Secondary: Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs</p>	<p>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.</p> <p>The number of participants in each category is reported in the table.</p>
<p>Secondary: Maximum observed blood concentration (C_{max}) of remibrutinib at Week 4 and Week 24</p>	<p>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.</p>

<p>Secondary: Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 4 and Week 24</p>	<p>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.</p>
<p>Secondary: Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 4 and Week 24</p>	<p>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.</p>
<p>Secondary: Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 4</p>	<p>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.</p>

Secondary: Elimination half-life (T1/2) of remibrutinib at Week 4	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.
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Test Product (s), Dose(s), and Mode(s) of Administration

The study drug is remibrutinib (LOU064). 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. 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.

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.

Statistical Methods

Analyses were produced using SAS version 9.4 or higher (SAS Institute, Cary NC). The analyses included only the Part 1 data as Part 2 was not conducted.

The analysis sets were as follows:

- Full Analysis Set (FAS): included all randomized patients, except those who were mis-randomized. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned at randomization.

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- **Safety Set:** included all patients who received at least one dose of the study drug. Patients were analyzed according to treatment received and the stratum they actually belong to in case of misallocation of strata during the randomization process. The safety set was used in the analysis of all safety variables.
- **PK Analysis Set:** included all patients with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug, and with no protocol deviations that impact PK data.

All patients within the FAS analysis set were included in the primary analysis for change from baseline in ESSDAI at Week 24. The ESSDAI score was listed by treatment group and visit/time. 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 (and including) Week 24 visit including baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix was fitted to model the dependency between repeated observations. Adjusted mean values of change from baseline were presented along with standard error. The difference in the mean change from baseline in ESSDAI at each visit between remibrutinib (qd and bid averaged) and placebo was estimated from the model and presented together with the associated 95% confidence intervals and one-sided p-value. In addition, the difference in the mean change from baseline in ESSDAI at each visit between remibrutinib dosing regimens (qd vs bid) was presented along with the associated 95% confidence intervals.

The following two criteria were used to assess treatment efficacy:

- a statistically significant decrease in ESSDAI at Week 24 on remibrutinib compared to placebo (at one-sided alpha level at 0.10) and
- an estimated mean change of at least 2 in ESSDAI at Week 24 on remibrutinib compared to placebo.

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Secondary endpoints of interest were: change from baseline for ESSPRI, FACIT-F, EQ VAS, and PhGA VAS; where a similar estimand framework as for the primary endpoint was adopted. The FAS analysis set was used for these secondary analyses. Similar to primary endpoint, a MMRM was fitted to the changes from baseline for corresponding secondary endpoint for all post-baseline time points up to (and including) Week 24 visit including baseline of the respective endpoint as a continuous covariate. The difference in the mean change from baseline of each secondary endpoint, at each visit between remibrutinib (qd and bid averaged) and placebo, was estimated from the model and presented together with the associated 95% confidence intervals and one-sided p-value. In addition, the difference in the mean change from baseline of each secondary endpoint, at each visit between remibrutinib dosing regimens (qd vs. bid), was presented along with the associated 95% CIs.

Study Population: Key Inclusion/Exclusion Criteria**Inclusion Criteria:**

- Diagnosis of SjS according to the 2016 ACR/EULAR criteria
- Screening ESSDAI (based on weighted score) ≥ 5 derived from 8 domains
- Screening ESSPRI ≥ 5
- Seropositive for anti-Ro/SSA antibodies at or within 3 months prior to screening
- Unstimulated salivary flow > 0 mL/min.

Exclusion Criteria:

- Sjögren's Syndrome overlap syndromes with another autoimmune disease as primary illness
- DMARDs or kinase inhibitors within 3 months prior to baseline above certain doses OR maintained during study
- Rituximab or other B cell depleting drug within 12 months of Screening .
- Current use of prednisone or equivalent > 15 mg/d or dose change within 2 weeks prior to Screening
- Use of medication known to cause, as a major side effect, dry mouth / eyes
- HIV, Hepatitis C, Hepatitis B, known or suspected history of an ongoing, chronic or recurrent infectious disease such as tuberculosis

Participant Flow Table
Overall Study

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Total
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)	Placebo group	
Started	24	25	24	73
Completed	17	17	21	55
Not Completed	7	8	3	18
Adverse Event	3	4	2	9
Lost to Follow-up	0	1	0	1
Physician Decision	2	1	1	4
Subject Decision	2	2	0	4

Baseline Characteristics

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo	Total
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)	Placebo group	
Number of Participants [units: participants]	24	25	24	73
Age Continuous (units: years) Mean ± Standard Deviation	49.5±15.21	54.8±10.51	51.0±13.94	51.8±13.34

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Sex: Female, Male

(units: participants)

Count of Participants (Not Applicable)

Female	24	24	23	71
Male	0	1	1	2

Race/Ethnicity, Customized

(units: participants)

Count of Participants (Not Applicable)

Asian	7	7	7	21
White	17	17	16	50
Unknown	0	1	0	1
Black or African American	0	0	1	1

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

(Time Frame: Baseline, Week 24)

	Remibrutinib 100 mg qd	Remibrutinib 100 mg bid	Any remibrutinib	Placebo
Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	24	48	24
Change from baseline in EULAR Sjögren's syndrome Disease Activity Index (ESSDAI) total score at Week 24 (units: score on scale) Least Squares Mean ± Standard Error	-4.70 ± 0.78	-3.70 ± 0.80	-4.20 ± 0.56	-1.34 ± 0.74

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Statistical Analysis

Groups	Any remibrutinib, Placebo	
P Value	0.002	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-2.86	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-4.71 to -1.01	

Statistical Analysis

Groups	Remibrutinib 100 mg bid, Remibrutinib 100 mg qd	
Method	Other MMRM	
Mean Difference (Final Values)	-1.00	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-3.24 to 1.25	

Secondary Outcome Result(s)

Change from baseline in ESSDAI total score over time

(Time Frame: Baseline, Week 2, Week 4, Week 8, Week 12, Week 16 and Week 20)

Remibrutinib 100 mg qd Remibrutinib 100 mg bid Any remibrutinib Placebo

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Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	24	48	24
Change from baseline in ESSDAI total score over time (units: score on scale) Least Squares Mean ± Standard Error				
Week 2	-1.68 ± 0.52	-1.05 ± 0.52	-1.37 ± 0.37	-0.37 ± 0.55
Week 4	-2.57 ± 0.60	-2.54 ± 0.62	-2.55 ± 0.43	-0.79 ± 0.61
Week 8	-2.74 ± 0.72	-2.93 ± 0.71	-2.83 ± 0.51	-2.36 ± 0.69
Week 12	-3.66 ± 0.74	-2.56 ± 0.75	-3.11 ± 0.53	-1.92 ± 0.73
Week 16	-4.02 ± 0.71	-2.57 ± 0.74	-3.29 ± 0.51	-2.16 ± 0.69
Week 20	-4.40 ± 0.73	-3.26 ± 0.75	-3.83 ± 0.52	-1.84 ± 0.69

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 2
P Value	0.065	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-0.99	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-2.29 to 0.30	

Statistical Analysis

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Groups	Any remibrutinib, Placebo	Week 4
P Value	0.010	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-1.76	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-3.24 to -0.29	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 8
P Value	0.289	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-0.47	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-2.17 to 1.22	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 12
P Value	0.093	one-sided p-value
Method	Other MMRM	

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Mean Difference (Final Values)	-1.19	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-2.97 to 0.59
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 16
P Value	0.094	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-1.13	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-2.84 to 0.57
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 20
P Value	0.012	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-1.99
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95 % Confidence Interval 2-Sided	-3.71 to -0.28
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Statistical Analysis

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Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 2
Method	Other MMRM	
Mean Difference (Final Values)	-0.63	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-2.10 to 0.84	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 4
Method	Other MMRM	
Mean Difference (Final Values)	-0.03	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.75 to 1.69	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 8
Method	Other MMRM	
Mean Difference (Final Values)	0.19	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.83 to 2.21	

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Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 12
Method	Other MMRM	
Mean Difference (Final Values)	-1.10	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-3.20 to 1.01	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 16
Method	Other MMRM	
Mean Difference (Final Values)	-1.45	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-3.50 to 0.60	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 20
Method	Other MMRM	
Mean Difference (Final Values)	-1.14	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

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95
 % Confidence Interval -3.22 to 0.95
 2-Sided

Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) total score over time
 (Time Frame: Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24)

	Remibrutinib 100 mg qd	Remibrutinib 100 mg bid	Any remibrutinib	Placebo
Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	24	48	24
Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) total score over time (units: score on scale) Least Squares Mean ± Standard Error				
Week 2	-0.44 ± 0.26	0.18 ± 0.26	-0.13 ± 0.18	-0.09 ± 0.27
Week 4	-0.72 ± 0.30	-0.14 ± 0.30	-0.43 ± 0.21	-0.35 ± 0.30
Week 8	-0.83 ± 0.31	-0.38 ± 0.31	-0.60 ± 0.22	-0.57 ± 0.29
Week 12	-0.88 ± 0.31	-0.32 ± 0.31	-0.60 ± 0.22	-0.66 ± 0.29
Week 16	-0.77 ± 0.36	-0.39 ± 0.37	-0.58 ± 0.26	-0.71 ± 0.34
Week 20	-0.92 ± 0.38	-0.74 ± 0.39	-0.83 ± 0.27	-0.92 ± 0.36
Week 24	-1.17 ± 0.34	-0.76 ± 0.35	-0.96 ± 0.24	-1.13 ± 0.31

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 2
P Value	0.460	one-sided p-value
Method	Other MMRM	

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Mean Difference (Final Values)	-0.03	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-0.69 to 0.62
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 4
P Value	0.418	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-0.08	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-0.82 to 0.66
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 8
P Value	0.466	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-0.03	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-0.76 to 0.70
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Statistical Analysis

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Groups	Any remibrutinib, Placebo	Week 12
P Value	0.560	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	0.06	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-0.67 to 0.79	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 16
P Value	0.616	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	0.13	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-0.73 to 0.99	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 20
P Value	0.581	one-sided p-value
Method	Other MMRM	

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Mean Difference (Final Values)	0.13
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95 % Confidence Interval 2-Sided	-0.81 to 0.99
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 24
P Value	0.663	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	0.17	Difference (Any remibrutinib - Placebo)

95 % Confidence Interval 2-Sided	-0.62 to 0.96
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Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 2
Method	Other MMRM	
Mean Difference (Final Values)	-0.62	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

95 % Confidence Interval 2-Sided	-1.35 to 0.11
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Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 4
Method	Other MMRM	
Mean Difference (Final Values)	-0.58	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.42 to 0.26	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 8
Method	Other MMRM	
Mean Difference (Final Values)	-0.45	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.31 to 0.42	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 12
Method	Other MMRM	
Mean Difference (Final Values)	-0.57	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.44 to 0.31	

Clinical Trial Results Website
Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 16
Method	Other MMRM	
Mean Difference (Final Values)	-0.37	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.39 to 0.65	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 20
Method	Other MMRM	
Mean Difference (Final Values)	-0.37	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-1.39 to 0.65	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 24
Method	Other MMRM	
Mean Difference (Final Values)	-0.40	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

Clinical Trial Results Website

95
 % Confidence Interval -1.37 to 0.57
 2-Sided

Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) total score over time
 (Time Frame: Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24)

	Remibrutinib 100 mg qd	Remibrutinib 100 mg bid	Any remibrutinib	Placebo
Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	23	47	23
Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) total score over time (units: score on scale) Least Squares Mean ± Standard Error				
Week 2	1.80 ± 1.32	-0.51 ± 1.35	0.64 ± 0.95	3.37 ± 1.43
Week 4	4.83 ± 1.50	3.97 ± 1.57	4.40 ± 1.09	3.51 ± 1.58
Week 8	4.00 ± 1.64	3.79 ± 1.66	3.90 ± 1.17	5.26 ± 1.60
Week 12	4.88 ± 1.80	4.25 ± 1.86	4.56 ± 1.30	7.30 ± 1.77
Week 16	4.40 ± 1.97	3.29 ± 2.08	3.84 ± 1.44	7.73 ± 1.98
Week 20	10.01 ± 2.20	4.32 ± 2.30	7.16 ± 1.60	5.77 ± 2.17
Week 24	8.17 ± 2.45	4.64 ± 2.55	6.40 ± 1.77	7.45 ± 2.32

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 2
P Value	0.940	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	-2.73	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-6.18 to 0.73	
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 4
P Value	0.322	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	0.89	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-2.95 to 4.74	
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 8
P Value	0.753	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-1.36	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-5.32 to 2.59	
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Statistical Analysis

Clinical Trial Results Website

Groups	Any remibrutinib, Placebo	Week 12
P Value	0.891	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-2.74	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-7.13 to 1.66	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 16
P Value	0.941	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-3.88	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-8.77 to 1.01	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 20
P Value	0.304	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	1.39
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95 % Confidence Interval 2-Sided	-4.01 to 6.79
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 24
P Value	0.640	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-1.05	Difference (Any remibrutinib - Placebo)

95 % Confidence Interval 2-Sided	-6.89 to 4.79
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Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 2
Method	Other MMRM	
Mean Difference (Final Values)	2.32	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

95 % Confidence Interval 2-Sided	-1.44 to 6.07
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Statistical Analysis

Clinical Trial Results Website

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 4
Method	Other MMRM	
Mean Difference (Final Values)	0.86	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-3.46 to 5.18	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 8
Method	Other MMRM	
Mean Difference (Final Values)	0.20	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-4.43 to 4.83	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 12
Method	Other MMRM	
Mean Difference (Final Values)	0.63	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-4.53 to 5.78	

Clinical Trial Results Website
Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 16
Method	Other MMRM	
Mean Difference (Final Values)	1.11	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-4.60 to 6.82	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 20
Method	Other MMRM	
Mean Difference (Final Values)	5.69	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-0.66 to 12.04	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 24
Method	Other MMRM	
Mean Difference (Final Values)	3.53	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

Clinical Trial Results Website

95
 % Confidence Interval -3.53 to 10.59
 2-Sided

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

(Time Frame: Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24)

	Remibrutinib 100 mg qd	Remibrutinib 100 mg bid	Any remibrutinib	Placebo
Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	23	47	23
Change from baseline in EuroQual 5 dimensions (EQ-5D) VAS score over time (units: score on scale) Least Squares Mean ± Standard Error				
Week 2	-3.05 ± 3.11	-2.86 ± 3.16	-2.95 ± 2.22	-3.02 ± 3.28
Week 4	-1.74 ± 2.71	-0.03 ± 2.86	-0.88 ± 1.97	2.99 ± 2.87
Week 8	1.46 ± 3.20	1.76 ± 3.20	1.61 ± 2.26	3.44 ± 3.04
Week 12	-2.36 ± 2.71	1.58 ± 2.82	-0.39 ± 1.95	4.00 ± 2.64
Week 16	-0.44 ± 3.27	4.27 ± 3.54	1.92 ± 2.41	1.79 ± 3.28
Week 20	-0.91 ± 3.15	5.37 ± 3.33	2.23 ± 2.29	5.29 ± 3.01
Week 24	1.81 ± 3.47	5.73 ± 3.65	3.77 ± 2.52	2.07 ± 3.22

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 2
P Value	0.494	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	0.06	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-7.84 to 7.96
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 4
P Value	0.866	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-3.87	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-10.81 to 3.06
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 8
P Value	0.684	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-1.82	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-9.37 to 5.73
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Statistical Analysis

Clinical Trial Results Website

Groups	Any remibrutinib, Placebo	Week 12
P Value	0.908	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	-4.39	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-10.93 to 2.14	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 16
P Value	0.487	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	0.13	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-8.00 to 8.26	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 20
P Value	0.790	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	-3.06
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95 % Confidence Interval 2-Sided	-10.61 to 4.49
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 24
P Value	0.340	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	1.70	Difference (Any remibrutinib - Placebo)

95 % Confidence Interval 2-Sided	-6.48 to 9.88
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Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 2
Method	Other MMRM	
Mean Difference (Final Values)	-0.19	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

95 % Confidence Interval 2-Sided	-9.06 to 8.68
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Statistical Analysis

Clinical Trial Results Website

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 4
Method	Other MMRM	
Mean Difference (Final Values)	-1.71	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-9.59 to 6.17	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 8
Method	Other MMRM	
Mean Difference (Final Values)	-0.30	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-9.34 to 8.74	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 12
Method	Other MMRM	
Mean Difference (Final Values)	-3.94	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-11.74 to 3.86	

Clinical Trial Results Website
Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 16
Method	Other MMRM	
Mean Difference (Final Values)	-4.71	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-14.34 to 4.93	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 20
Method	Other MMRM	
Mean Difference (Final Values)	-6.29	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-15.44 to 2.87	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 24
Method	Other MMRM	
Mean Difference (Final Values)	-3.92	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

Clinical Trial Results Website

95
 % Confidence Interval -14.01 to 6.16
 2-Sided

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

(Time Frame: Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24)

	Remibrutinib 100 mg qd	Remibrutinib 100 mg bid	Any remibrutinib	Placebo
Arm/Group Description	Remibrutinib 100 mg once daily (qd)	Remibrutinib 100 mg twice daily (bid)	Patients in any of the two remibrutinib treatment groups	Placebo group
Number of Participants Analyzed [units: participants]	24	24	48	24
Change from baseline in Physician Global Assessment Scale (PhGA) score over time (units: score on scale) Least Squares Mean ± Standard Error				
Week 2	-4.21 ± 2.90	-4.02 ± 2.85	-4.12 ± 2.04	-4.82 ± 3.10
Week 4	-9.58 ± 2.89	-8.93 ± 2.96	-9.26 ± 2.08	-7.28 ± 2.95
Week 8	-13.68 ± 3.39	-13.78 ± 3.28	-13.73 ± 2.37	-13.23 ± 3.16
Week 12	-13.85 ± 3.63	-9.45 ± 3.68	-11.65 ± 2.60	-17.67 ± 3.52
Week 16	-19.37 ± 3.61	-7.25 ± 3.74	-13.31 ± 2.61	-15.90 ± 3.51
Week 20	-23.56 ± 3.43	-17.31 ± 3.48	-20.43 ± 2.45	-17.57 ± 3.20
Week 24	-21.25 ± 3.88	-13.15 ± 3.95	-17.20 ± 2.78	-20.15 ± 3.54

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 2
P Value	0.575	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	0.71	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-6.75 to 8.16
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 4
P Value	0.294	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-1.98	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-9.22 to 5.27
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 8
P Value	0.450	one-sided p-value
Method	Other MMRM	

Mean Difference (Final Values)	-0.50	Difference (Any remibrutinib - Placebo)
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95 % Confidence Interval 2-Sided	-8.40 to 7.41
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Statistical Analysis

Clinical Trial Results Website

Groups	Any remibrutinib, Placebo	Week 12
P Value	0.913	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	6.02	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-2.74 to 14.78	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 16
P Value	0.722	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	2.59	Difference (Any remibrutinib - Placebo)
95 % Confidence Interval 2-Sided	-6.16 to 11.34	

Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 20
P Value	0.241	one-sided p-value
Method	Other MMRM	

Clinical Trial Results Website

Mean Difference (Final Values)	-2.86
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95 % Confidence Interval 2-Sided	-10.96 to 5.24
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Statistical Analysis

Groups	Any remibrutinib, Placebo	Week 24
P Value	0.742	one-sided p-value
Method	Other MMRM	
Mean Difference (Final Values)	2.95	Difference (Any remibrutinib - Placebo)

95 % Confidence Interval 2-Sided	-6.09 to 11.99
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Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 2
Method	Other MMRM	
Mean Difference (Final Values)	-0.18	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

95 % Confidence Interval 2-Sided	-8.28 to 7.91
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Statistical Analysis

Clinical Trial Results Website

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 4
Method	Other MMRM	
Mean Difference (Final Values)	-0.65	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-8.87 to 7.58	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 8
Method	Other MMRM	
Mean Difference (Final Values)	0.10	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-9.28 to 9.48	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 12
Method	Other MMRM	
Mean Difference (Final Values)	-4.40	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-14.71 to 5.90	

Clinical Trial Results Website
Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 16
Method	Other MMRM	
Mean Difference (Final Values)	-12.1	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-22.47 to -1.77	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 20
Method	Other MMRM	
Mean Difference (Final Values)	-6.25	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)
95 % Confidence Interval 2-Sided	-16.00 to 3.50	

Statistical Analysis

Groups	Remibrutinib 100 mg qd, Remibrutinib 100 mg bid	Week 24
Method	Other MMRM	
Mean Difference (Final Values)	-8.10	Difference (remibrutinib 100 mg qd - remibrutinib 100 mg bid)

Clinical Trial Results Website

95
 % Confidence Interval -19.16 to 2.96
 2-Sided

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

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

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd	Placebo
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)	Placebo group
Number of Participants Analyzed [units: participants]	24	25	24
Number of participants with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs (units: participants) Count of Participants (Not Applicable)			
TEAE	22 (91.67%)	21 (84%)	20 (83.33%)
Study drug-related TEAE	10 (41.67%)	8 (32%)	9 (37.5%)
Serious TEAE	1 (4.17%)	1 (4%)	1 (4.17%)

Maximum observed blood concentration (Cmax) of remibrutinib at Week 4

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	16	13
Maximum observed blood concentration (Cmax) of remibrutinib at Week 4 (units: ng/mL) Mean ± Standard Deviation		
	183 ± 82.5	225 ± 154

Maximum observed blood concentration (Cmax) of remibrutinib at Week 24

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	14	10
Maximum observed blood concentration (Cmax) of remibrutinib at Week 24 (units: ng/mL) Mean ± Standard Deviation		
	224 ± 202	169 ± 77.9

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	16	13
Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 4 (units: hours) Median (Full Range)		
	1.00 (0.500 to 3.00)	1.00 (0.500 to 4.00)

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24)

Clinical Trial Results Website

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	14	10
Time to reach maximum observed blood concentration (Tmax) of remibrutinib at Week 24 (units: hours) Median (Full Range)		
	1.00 (0.500 to 3.00)	1.00 (0.500 to 3.08)

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	16	8
Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 4 (units: h*ng/mL) Mean ± Standard Deviation		
	569 ± 311	1020 ± 700

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	14	6
Area under the blood concentration-time curve within a dosing interval (tau) at steady-state (AUCtau) of remibrutinib at Week 24 (units: h*ng/mL) Mean ± Standard Deviation	670 ± 380	636 ± 306

Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 4
(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	16	13
Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 4 (units: h*ng/mL) Mean ± Standard Deviation	351 ± 169	393 ± 207

Area under the blood concentration-time curve from time zero to 4 hours post-dose (AUC0-4h) of remibrutinib at Week 24
(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	14	10

Clinical Trial Results Website

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

(units: h*ng/mL)

Mean ± Standard Deviation

420 ± 259	317 ± 144
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Elimination half-life (T1/2) of remibrutinib at Week 4

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 4)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	11	9
Elimination half-life (T1/2) of remibrutinib at Week 4 (units: hours) Mean ± Standard Deviation	3.08 ± 0.998	3.86 ± 2.28

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

(Time Frame: pre-dose, 0.5, 1, 2, 3 and 4 hours post-dose at Week 24)

	Remibrutinib 100 mg bid	Remibrutinib 100 mg qd
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg once daily (qd)
Number of Participants Analyzed [units: participants]	11	8
Elimination half-life (T1/2) of remibrutinib at Week 24 (units: hours) Mean ± Standard Deviation	3.15 ± 0.907	3.88 ± 1.95

Safety Results

All-Cause Mortality

	Remibrutinib 100 mg bid N = 24	Remibrutinib 100 mg qd N = 25	Any remibrutinib N = 49	Placebo N = 24	Total N = 73
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg qd	Patients in any of the two remibrutinib treatment groups	Placebo group	All participants
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	From first dose of study treatment up 30 days after last dose (Week 29)
Additional Description	Any sign or symptom that occurs from first dose of study treatment up to 30 days after last dose.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

	Remibrutinib 100 mg bid N = 24	Remibrutinib 100 mg qd N = 25	Any remibrutinib N = 49	Placebo N = 24	Total N = 73
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg qd	Patients in any of the two remibrutinib treatment groups	Placebo group	All participants

Clinical Trial Results Website

Total participants affected	1 (4.17%)	1 (4.00%)	2 (4.08%)	1 (4.17%)	3 (4.11%)
Infections and infestations					
COVID-19 pneumonia	1 (4.17%)	0 (0.00%)	1 (2.04%)	0 (0.00%)	1 (1.37%)
Herpes zoster	0 (0.00%)	1 (4.00%)	1 (2.04%)	0 (0.00%)	1 (1.37%)
Pneumonia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (4.17%)	1 (1.37%)

Other Adverse Events by System Organ Class

Time Frame	From first dose of study treatment up 30 days after last dose (Week 29)
Additional Description	Any sign or symptom that occurs from first dose of study treatment up to 30 days after last dose.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Remibrutinib 100 mg bid N = 24	Remibrutinib 100 mg qd N = 25	Any remibrutinib N = 49	Placebo N = 24	Total N = 73
Arm/Group Description	Remibrutinib 100 mg twice daily (bid)	Remibrutinib 100 mg qd	Patients in any of the two remibrutinib treatment groups	Placebo group	All participants
Total participants affected	15 (62.50%)	12 (48.00%)	27 (55.10%)	17 (70.83%)	44 (60.27%)
Blood and lymphatic system disorders					
Leukopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (12.50%)	3 (4.11%)

Clinical Trial Results Website

Lymphopenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (12.50%)	3 (4.11%)
Neutropenia	1 (4.17%)	1 (4.00%)	2 (4.08%)	2 (8.33%)	4 (5.48%)
Gastrointestinal disorders					
Abdominal distension	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.74%)
Abdominal pain	1 (4.17%)	2 (8.00%)	3 (6.12%)	1 (4.17%)	4 (5.48%)
Diarrhoea	2 (8.33%)	0 (0.00%)	2 (4.08%)	1 (4.17%)	3 (4.11%)
Nausea	4 (16.67%)	1 (4.00%)	5 (10.20%)	2 (8.33%)	7 (9.59%)
General disorders and administration site conditions					
Asthenia	0 (0.00%)	2 (8.00%)	2 (4.08%)	1 (4.17%)	3 (4.11%)
Fatigue	3 (12.50%)	0 (0.00%)	3 (6.12%)	2 (8.33%)	5 (6.85%)
Infections and infestations					
Nasopharyngitis	2 (8.33%)	1 (4.00%)	3 (6.12%)	3 (12.50%)	6 (8.22%)
Sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.74%)
Upper respiratory tract infection	3 (12.50%)	0 (0.00%)	3 (6.12%)	2 (8.33%)	5 (6.85%)
Urinary tract infection	1 (4.17%)	1 (4.00%)	2 (4.08%)	2 (8.33%)	4 (5.48%)
Injury, poisoning and procedural complications					
Fall	2 (8.33%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (2.74%)
Investigations					

Clinical Trial Results Website

Blood immunoglobulin G increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.74%)
White blood cell count decreased	2 (8.33%)	1 (4.00%)	3 (6.12%)	0 (0.00%)	3 (4.11%)
Metabolism and nutrition disorders					
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (8.33%)	2 (2.74%)
Musculoskeletal and connective tissue disorders					
Arthralgia	1 (4.17%)	2 (8.00%)	3 (6.12%)	1 (4.17%)	4 (5.48%)
Back pain	0 (0.00%)	2 (8.00%)	2 (4.08%)	2 (8.33%)	4 (5.48%)
Muscle spasms	0 (0.00%)	2 (8.00%)	2 (4.08%)	0 (0.00%)	2 (2.74%)
Myalgia	0 (0.00%)	1 (4.00%)	1 (2.04%)	2 (8.33%)	3 (4.11%)
Sjogren's syndrome	2 (8.33%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (2.74%)
Nervous system disorders					
Headache	1 (4.17%)	3 (12.00%)	4 (8.16%)	5 (20.83%)	9 (12.33%)
Skin and subcutaneous tissue disorders					
Petechiae	2 (8.33%)	0 (0.00%)	2 (4.08%)	0 (0.00%)	2 (2.74%)

Conclusion:

The researchers concluded that after finishing 24 weeks of treatment, the participants who took either dose of remibrutinib had meaningfully lower ESSDAI scores than those who took placebo. ESSDAI scores were also meaningfully decreasing over time during the 20 weeks of treatment. The researchers found no new safety concerns for remibrutinib in this trial.

Using ESSPRI, FACIT-F, EQ-5D, and PhGA, the researchers also learned that after 24 weeks of treatment, there was no meaningful difference in:

- overall SjS symptom severity and condition between the remibrutinib and placebo groups
- quality of life of participants between the remibrutinib and placebo groups

As expected, total exposure over 24 h (AUC) was about double for the remibrutinib 100 mg bid group compared to the remibrutinib 100 mg qd group, with similar mean C_{max} and median T_{max} and fast elimination, nearly returning to baseline levels prior to each new dose. The PK profile was comparable to historical data and not meaningfully different to other target populations.

Overall, the results of Part 1 confirm the potential of remibrutinib as a treatment in Sjögren's syndrome. Efficacy and safety data confirm a positive benefit-risk and support continued development of remibrutinib across indications and in Sjögren's syndrome.

Date of Clinical Trial Report

5-Oct-2022