



Clinical trial results:

A multi-center, randomized, participant- and investigator- blinded, placebo-controlled, parallel group basket study to evaluate the safety, tolerability and efficacy of MHV370 in participants with Sjögren's Syndrome or Mixed Connective Tissue Disease

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-004937-19 |
| Trial protocol | DE ES HU |
| Global end of trial date | 07 March 2023 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 February 2024 |
| First version publication date | 01 February 2024 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CMHV370A12201 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04988087 |
| 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 | 07 March 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 07 March 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:

- To evaluate the efficacy of MHV370 compared to placebo based on change from baseline in ESSDAI [EULAR (European League against Rheumatism) Sjogren's Syndrome Disease Activity Index] in SjS (Sjogren's Syndrome) participants
- To evaluate the efficacy of MHV370 compared to placebo based on change from baseline in Physician Global Assessment (PhGA) in MCTD (Mixed Connective Tissue Disease) participants.

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 | 30 November 2021 |
| 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 | China: 2 |
| Country: Number of subjects enrolled | Taiwan: 4 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Hungary: 5 |
| Country: Number of subjects enrolled | Spain: 1 |
| Country: Number of subjects enrolled | Poland: 9 |
| Worldwide total number of subjects | 30 |
| EEA total number of subjects | 24 |

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) | 28 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in 10 investigative sites in 6 countries/regions.

Pre-assignment

Screening details:

There was a screening period of up to 6 weeks to assess participants eligibility.

Period 1

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

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | MHV370 200mg - SjS |

Arm description:

MHV370 200mg oral dose, twice daily. SjS participants.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | MHV370 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

MHV370 200 mg oral twice daily - SjS participants

| | |
|------------------|---------------|
| Arm title | Placebo - SjS |
|------------------|---------------|

Arm description:

Placebo oral dose, twice daily. SjS participants.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | MHV370 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo oral twice daily - SjS participants

| | |
|------------------|---------------------|
| Arm title | MHV370 200mg - MCTD |
|------------------|---------------------|

Arm description:

MHV370 200mg oral dose, twice daily. MCTD participants.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | MHV370 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

MHV370 200 mg oral twice daily - MCTD participants

| | |
|--|----------------|
| Arm title | Placebo - MCTD |
| Arm description: | |
| Placebo oral dose, twice daily. MCTD participants. | |
| Arm type | Placebo |
| Investigational medicinal product name | MHV370 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo oral twice daily - MCTD participants

| Number of subjects in period 1 | MHV370 200mg - SJS | Placebo - SJS | MHV370 200mg - MCTD |
|---------------------------------------|--------------------|---------------|---------------------|
| Started | 12 | 14 | 2 |
| Completed | 0 | 4 | 1 |
| Not completed | 12 | 10 | 1 |
| Consent withdrawn by subject | 1 | 1 | - |
| Adverse events | 4 | - | - |
| Technical problems | 7 | 9 | 1 |

| Number of subjects in period 1 | Placebo - MCTD |
|---------------------------------------|----------------|
| Started | 2 |
| Completed | 0 |
| Not completed | 2 |
| Consent withdrawn by subject | - |
| Adverse events | - |
| Technical problems | 2 |

Baseline characteristics

Reporting groups

| | |
|---|---------------------|
| Reporting group title | MHV370 200mg - SjS |
| Reporting group description: MHV370 200mg oral dose, twice daily. SjS participants. | |
| Reporting group title | Placebo - SjS |
| Reporting group description: Placebo oral dose, twice daily. SjS participants. | |
| Reporting group title | MHV370 200mg - MCTD |
| Reporting group description: MHV370 200mg oral dose, twice daily. MCTD participants. | |
| Reporting group title | Placebo - MCTD |
| Reporting group description: Placebo oral dose, twice daily. MCTD participants. | |

| Reporting group values | MHV370 200mg - SjS | Placebo - SjS | MHV370 200mg - MCTD |
|--|--------------------|---------------|---------------------|
| Number of subjects | 12 | 14 | 2 |
| 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) | 11 | 13 | 2 |
| From 65-84 years | 1 | 1 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 49.3 | 54.7 | 35.0 |
| standard deviation | ± 12.20 | ± 9.67 | ± 12.73 |
| Sex: Female, Male Units: participants | | | |
| Female | 12 | 14 | 2 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 3 | 3 | 0 |
| White | 9 | 11 | 2 |

| Reporting group values | Placebo - MCTD | Total | |
|------------------------------------|----------------|-------|--|
| Number of subjects | 2 | 30 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |

| | | | |
|---|--------|----|--|
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 2 | 28 | |
| From 65-84 years | 0 | 2 | |
| 85 years and over | 0 | 0 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 44.0 | | |
| standard deviation | ± 0.00 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 2 | 30 | |
| Male | 0 | 0 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 0 | 6 | |
| White | 2 | 24 | |

End points

End points reporting groups

| | |
|---|---------------------|
| Reporting group title | MHV370 200mg - SjS |
| Reporting group description: MHV370 200mg oral dose, twice daily. SjS participants. | |
| Reporting group title | Placebo - SjS |
| Reporting group description: Placebo oral dose, twice daily. SjS participants. | |
| Reporting group title | MHV370 200mg - MCTD |
| Reporting group description: MHV370 200mg oral dose, twice daily. MCTD participants. | |
| Reporting group title | Placebo - MCTD |
| Reporting group description: Placebo oral dose, twice daily. MCTD participants. | |

Primary: SjS participants: Change from baseline in Eular Sjögren's Disease Activity Index (ESSDAI) after 24 weeks of treatment

| | |
|--|---|
| End point title | SjS participants: Change from baseline in Eular Sjögren's Disease Activity Index (ESSDAI) after 24 weeks of treatment ^{[1][2]} |
| End point description: The ESSDAI is an established disease outcome measure for Sjögren's syndrome that classifies disease activity in 3-4 levels according to their severity (i.e., no, low, moderate, high), over each of 12 organ-specific domains. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The score range is 0 - 123, where a higher ESSDAI score indicates more severe symptoms. A negative change score from baseline indicates improvement. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 24 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Endpoint specific to and only reported for SjS participants

[2] - 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: Endpoint specific to and only reported for SjS participants

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|----------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[3] | 4 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard error) | () | -4.39 (± 2.41) | | |

Notes:

[3] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Primary: MCTD participants: Change from baseline in physician's global assessment scale (PhGA) after 24 weeks of treatment

| | |
|-----------------|---|
| End point title | MCTD participants: Change from baseline in physician's global assessment scale (PhGA) after 24 weeks of treatment ^{[4][5]} |
|-----------------|---|

End point description:

The physician's global assessment scale is 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 score from baseline indicates improvement. Only participants with evaluable records are included.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Week 24

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Endpoint specific to and only reported for MCTD participants

[5] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|-------------------------------|------------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[6] | | |
| Units: Score on scale | | | | |
| median (full range (min-max)) | -62.00 (-62.00 to -62.00) | (to) | | |

Notes:

[6] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Secondary: SjS and MCTD participants: Maximum observed plasma concentrations (Cmax) of MHV370 at steady state

| | |
|-----------------|---|
| End point title | SjS and MCTD participants: Maximum observed plasma concentrations (Cmax) of MHV370 at steady state ^[7] |
|-----------------|---|

End point description:

Cmax is the maximum (peak) observed plasma concentration of MHV370 after single dose administration. Pharmacokinetic (PK) parameters were calculated based on MHV370 plasma concentrations determined by a validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1.0 ng/mL. Cmax was determined using non-compartmental methods. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

pre-dose, 0.5, 1, 2 ,4 and 6 hours after dosing at week 4

Notes:

[7] - 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 Endpoint not analyzed for participants on placebo

| End point values | MHV370 200mg - SjS | MHV370 200mg - MCTD | | |
|--------------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 1 | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | 278 (± 85.7) | 194 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS and MCTD participants: Area under the plasma concentration-time curve from time zero to 6 hours (AUC0-6h) of MHV370

| | |
|-----------------|--|
| End point title | SjS and MCTD participants: Area under the plasma concentration-time curve from time zero to 6 hours (AUC0-6h) of MHV370 ^[8] |
|-----------------|--|

End point description:

The AUC from time zero to the 6-hours post-dose sampling time. Pharmacokinetic (PK) parameters were calculated based on MHV370 plasma concentrations determined by a validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1.0 ng/mL. AUClast was determined using non-compartmental methods. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

pre-dose, 0.5, 1, 2 ,4 and 6 hours after dosing at week 4

Notes:

[8] - 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 Endpoint not analyzed for participants on placebo

| End point values | MHV370 200mg - SjS | MHV370 200mg - MCTD | | |
|--------------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 1 | | |
| Units: ng*h/mL | | | | |
| arithmetic mean (standard deviation) | 1060 (± 462) | 742 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS and MCTD participants: Time to reach maximum plasma concentrations (Tmax) of MHV370 at steady state

| | |
|-----------------|--|
| End point title | SjS and MCTD participants: Time to reach maximum plasma concentrations (Tmax) of MHV370 at steady state ^[9] |
|-----------------|--|

End point description:

Tmax is the time to reach maximum (peak) plasma concentration of MHV370 after single dose administration. Pharmacokinetic (PK) parameters were calculated based on MHV370 plasma concentrations determined by a validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1.0 ng/mL. Tmax was determined using non-

compartmental methods. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

pre-dose, 0.5, 1, 2 ,4 and 6 hours after dosing at week 4

Notes:

[9] - 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 Endpoint not analyzed for participants on placebo

| End point values | MHV370 200mg - SjS | MHV370 200mg - MCTD | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 1 | | |
| Units: hours | | | | |
| median (full range (min-max)) | 1.50 (1.00 to 4.00) | 2.00 (000 to 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS and MCTD participants: Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale

| | |
|-----------------|---|
| End point title | SjS and MCTD participants: Change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale |
|-----------------|---|

End point description:

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F v4) is a short, 13-item patient-reported measure, 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 is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). To score the FACIT-fatigue, all items are summed to create a single fatigue score with a range from 0 to 52, where a higher FACIT-F score indicates more severe symptoms. A negative change score from baseline indicates improvement. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 20 and 24

| End point values | MHV370 200mg - SjS | Placebo - SjS | MHV370 200mg - MCTD | Placebo - MCTD |
|--------------------------------------|-----------------------|-----------------|------------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8 | 12 | 2 | 1 |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 0.13 (± 3.271) | -1.58 (± 6.052) | 15.50 (± 9.192) | -3.00 (± 999) |
| Week 8 (n= 7,10,2,1) | 3.14 (± 5.928) | -2.80 (± 4.185) | 20.00 (± 7.071) | -2.00 (± 999) |

| | | | | |
|----------------------|-----------------|-----------------|---------------|-------------|
| Week 12 (n= 4,7,1,0) | -1.25 (± 6.702) | 2.71 (± 8.826) | 20.00 (± 999) | 999 (± 999) |
| Week 20 (n= 1,5,1,0) | -9.42 (± 999) | 4.80 (± 8.758) | 23.00 (± 999) | 999 (± 999) |
| Week 24 (n= 0,4,1,0) | 999 (± 999) | 5.75 (± 10.782) | 30.00 (± 999) | 999 (± 999) |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS and MCTD participants: Change from baseline in Physician Global Assessment (PhGA)

| | |
|-----------------|---|
| End point title | SjS and MCTD participants: Change from baseline in Physician Global Assessment (PhGA) |
|-----------------|---|

End point description:

The physician's global assessment scale is 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 score from baseline indicates improvement. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 20 and 24

| End point values | MHV370 200mg - SjS | Placebo - SjS | MHV370 200mg - MCTD | Placebo - MCTD |
|--------------------------------------|-----------------------|-------------------|------------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 8 | 12 | 2 | 1 |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -1.75 (± 12.658) | -5.25 (± 11.185) | -20.50 (± 12.021) | -15.00 (± 999) |
| Week 8 (n= 7,10,2,1) | 2.57 (± 12.608) | -8.90 (± 11.474) | -39.00 (± 18.385) | -12.50 (± 999) |
| Week 12 (n= 4,7,1,0) | -4.00 (± 20.559) | -19.43 (± 14.328) | -66.00 (± 999) | 999 (± 999) |
| Week 20 (n= 1,5,1,0) | 3.00 (± 999) | -14.60 (± 22.423) | -64.00 (± 999) | 999 (± 999) |
| Week 24 (n= 0,4,1,0) | 999 (± 999) | -30.75 (± 19.534) | -62.00 (± 999) | 999 (± 999) |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS participants: Change from baseline in Euler Sjögren's Syndrome Disease Activity Index (ESSDAI)

| | |
|--|--|
| End point title | SjS participants: Change from baseline in Eular Sjögren's Syndrome Disease Activity Index (ESSDAI) ^[10] |
| End point description: | |
| <p>The ESSDAI is an established disease outcome measure for Sjögren's syndrome that classifies disease activity in 3-4 levels according to their severity (i.e., no, low, moderate, high), over each of 12 organ-specific domains. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The score range is 0 - 123, where a higher ESSDAI score indicates more severe symptoms. A negative change score from baseline indicates improvement. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.</p> <p>The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 8, 12, 20 and 24 | |

Notes:

[10] - 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: Endpoint specific to and only reported for SjS participants

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|--------------------------------------|-----------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -0.25 (± 1.753) | -3.67 (± 9.355) | | |
| Week 8 (n= 7,10) | 0.57 (± 6.528) | -4.80 (± 11.487) | | |
| Week 12 (n= 3,7) | -3.00 (± 4.583) | -3.43 (± 7.656) | | |
| Week 20 (n= 1,5) | -2.00 (± 999) | 0.00 (± 14.629) | | |
| Week 24 (n= 0,4) | 999 (± 999) | -0.25 (± 11.117) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS participants: Change from baseline in Eular Sjögren's Syndrome Patient Reported Index (ESSPRI)

| | |
|---|--|
| End point title | SjS participants: Change from baseline in Eular Sjögren's Syndrome Patient Reported Index (ESSPRI) ^[11] |
| End point description: | |
| <p>The ESSPRI is a disease outcome measure for Sjögren's syndrome. The ESSPRI is a patient-reported, subjective symptom index which consists of three questions covering the cardinal symptoms of Sjögren's syndrome: dryness, fatigue and pain (articular and/or muscular). The participant can assess severity of symptoms they experience on a single numerical scale of 0-10 (0=no symptom at all and 10= worst symptom imaginable) for each of the three domains. The overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Min. score can be 0 and max. score can be 10, where a higher score indicates severe symptoms. A negative change score from baseline indicates improvement. Due to system limitations, data fields in the table cannot contain letters. Therefore, not applicable values are indicated as '999'. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.</p> | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| baseline, weeks 4, 8, 12, 20 and 24 | |
| Notes: | |
| [11] - 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: Endpoint specific to and only reported for SjS participants | |

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|--------------------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | -0.12 (± 0.354) | -0.53 (± 1.105) | | |
| Week 8 (n= 7,10) | -0.67 (± 0.793) | -0.37 (± 1.511) | | |
| Week 12 (n= 4,7) | -0.42 (± 0.500) | -1.38 (± 1.976) | | |
| Week 20 (n= 1,5) | -0.17 (± 999) | -2.20 (± 1.865) | | |
| Week 24 (n= 0,4) | 999 (± 999) | -2.00 (± 2.000) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS participants: Change from baseline to the salivary flow rate

| | |
|--|---|
| End point title | SjS participants: Change from baseline to the salivary flow |
| End point description: | |
| <p>Unstimulated whole salivary fluid secretions were collected over 5 minutes from participants. All assessments were performed at a fixed time of the day to minimize fluctuations related to the circadian rhythm of salivary flow and composition. Participants were instructed not to eat, drink or smoke for 90 minutes before the assessment. The start time and end time of saliva collection were recorded to calculate the salivary flow rate per minute. Only participants with evaluable records are included. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.</p> <p>The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 12 and 24 | |
| Notes: | |
| [12] - 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: Endpoint specific to and only reported for SjS participants | |

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|--------------------------------------|-----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 14 | | |
| Units: mL/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 0.162 (± 0.2735) | -0.127 (± 0.7914) | | |
| Week 12 (n= 4,7) | 0.144 (± 0.2109) | 0.183 (± 0.3944) | | |
| Week 24 (n= 0,4) | 999 (± 999) | 0.564 (± 0.9193) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS participants: Change from baseline to the Schirmer's test

| | |
|-----------------|--|
| End point title | SjS participants: Change from baseline to the Schirmer's |
|-----------------|--|

End point description:

Schirmer's test is used to determine whether the eye produces enough tears to keep it moist especially for those who suffer from dry eye syndrome. A strip is placed in the lower eyelid for 5 minutes to assess tear production. After 5 minutes, the filter paper is removed and the distance between the leading edge of wetness and the initial fold is measured, using a millimeter ruler. Tear deficiency is defined as <5 mm wetting of the paper after 5 minutes. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 4, 12 and 24

Notes:

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

Justification: Endpoint specific to and only reported for SjS participants

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|--------------------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 14 | | |
| Units: milimeter | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4, right eye (n= 8,12) | -1.5 (± 4.87) | 0.0 (± 3.59) | | |
| Week 12, right eye (n= 4,7) | -1.0 (± 2.16) | 5.3 (± 8.81) | | |
| Week 24, right eye (n= 0,4) | 999 (± 999) | -3.0 (± 6.32) | | |
| Week 4, left eye (n= 8,12) | 1.1 (± 1.96) | 1.6 (± 6.01) | | |
| Week 12, left eye (n= 4,7) | 2.0 (± 1.83) | 4.9 (± 12.50) | | |
| Week 24, left eye (n= 0,4) | 999 (± 999) | -1.0 (± 2.94) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SjS participants: Sjögren's Tool for Assessing Response (STAR) response over time up to week 24

| | |
|-----------------|---|
| End point title | SjS participants: Sjögren's Tool for Assessing Response (STAR) response over time up to week 24 ^[14] |
|-----------------|---|

End point description:

STAR is a composite responder index, including in a single tool all main disease features, and designed for use as a key efficacy endpoint in SjS Domain Point Definition of response.

Points are assigned in the following 5 domains, if the corresponding criteria are met:

- Systemic activity, if decrease in clin ESSDAI ≥ 3 points: 3 points
- Patient reported outcome, if decrease in ESSPRI ≥ 1 point or 15%: 3 points
- Lacrimal gland function (assessed by Schirmer's test), if abnormal score at baseline: increase ≥ 5 mm from baseline OR if normal score at baseline: no change to abnormal: 1 point
- Salivary gland function (assessed by unstimulated salivary flow), if increase $\geq 25\%$ from baseline: 1 point
- Biological (assessed by serum IgG levels), if decrease $\geq 10\%$: 1 point

The Total Score is the sum of all 5 domain scores, ranging from 0 to 9 points. A STAR responder is defined as ≥ 5 points in the Total Score.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 4, 12 and 24

Notes:

[14] - 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: Endpoint specific to and only reported for SjS participants

| End point values | MHV370 200mg - SjS | Placebo - SjS | | |
|-----------------------------|-----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 14 | | |
| Units: participants | | | | |
| Week 4 | 0 | 3 | | |
| Week 12 | 1 | 4 | | |
| Week 24 | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD: Change from baseline in articular and pulmonary domains of the Eular Sjögren's Syndrome Disease Activity Index (ESSDAI)

| | |
|-----------------|---|
| End point title | MCTD: Change from baseline in articular and pulmonary domains of the Eular Sjögren's Syndrome Disease Activity Index (ESSDAI) ^[15] |
|-----------------|---|

End point description:

The ESSDAI is an established disease outcome measure for Sjögren's syndrome that classifies disease activity in 3-4 levels according to their severity (i.e., no, low, moderate, high), over each of 12 organ-specific domains. Participants with Mixed Connective Tissue Disease (MCTD) completed the articular (from 0 "no activity" to 3 "high activity") and pulmonary (from 0 "no activity" to 3 "high activity") domains of the ESSDAI only. For MCTD participants, the score range is 0-21, where a higher score indicates more severe symptoms. A negative change score from baseline indicates improvement. Due to

EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.
The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|---------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 8, 12 and 24 | |

Notes:

[15] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 1 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 - articular | 0.00 (± 0.000) | 0.00 (± 999) | | |
| Week 8 - articular | -1.00 (± 0.000) | 0.00 (± 999) | | |
| Week 12 - articular (n= 1,0) | -1.00 (± 999) | 999 (± 999) | | |
| Week 24 - articular (n= 1,0) | -2.00 (± 999) | 999 (± 999) | | |
| Week 4 - pulmonary | 0.00 (± 0.000) | 0.00 (± 999) | | |
| Week 8 - pulmonary | -0.50 (± 0.707) | 0.00 (± 999) | | |
| Week 12 - pulmonary (n= 1,0) | -1.00 (± 999) | 999 (± 999) | | |
| Week 24 - pulmonary (n= 1,0) | -1.00 (± 999) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in Forced expiratory volume during the first second (FEV1) of a forced breath

| | |
|-----------------|---|
| End point title | MCTD participants: Change from baseline in Forced expiratory volume during the first second (FEV1) of a forced breath ^[16] |
|-----------------|---|

End point description:

FEV1 (forced expiratory volume in one second) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. A positive change from baseline in FEV1 is considered a favourable outcome. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |

Notes:

[16] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[17] | | |
| Units: liters (L) | | | | |
| arithmetic mean (standard deviation) | 0.250 (± 999) | () | | |

Notes:

[17] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in Forced Vital Capacity (FVC)

| | |
|-----------------|--|
| End point title | MCTD participants: Change from baseline in Forced Vital Capacity (FVC) ^[18] |
|-----------------|--|

End point description:

Forced Vital Capacity (FVC) is the total amount of air exhaled during the Forced expiratory volume (FEV) test measured through spirometry testing. FEV measures how much air a person can exhale during a forced breath. A positive change from baseline is considered a favorable outcome. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 12

Notes:

[18] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[19] | | |
| Units: liters (L) | | | | |
| arithmetic mean (standard deviation) | 0.530 (± 999) | () | | |

Notes:

[19] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in Forced expiratory volume during the first two seconds (FEV2) of a forced breath

| | |
|-----------------|--|
| End point title | MCTD participants: Change from baseline in Forced expiratory volume during the first two seconds (FEV2) of a forced breath ^[20] |
|-----------------|--|

End point description:

FEV2 (forced expiratory volume in two seconds) is the amount of air which can be forcibly exhaled from the lungs in the first two seconds of a forced exhalation, measured through spirometry testing. A positive change from baseline in FEV2 is considered a favourable outcome. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |
| Notes: | |
| [20] - 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: Endpoint specific to and only reported for MCTD participants | |

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[21] | | |
| Units: liters (L) | | | | |
| arithmetic mean (standard deviation) | 0.410 (± 999) | () | | |

Notes:

[21] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in Forced expiratory volume during the first three seconds (FEV3) of a forced breath

| | |
|-----------------|--|
| End point title | MCTD participants: Change from baseline in Forced expiratory volume during the first three seconds (FEV3) of a forced breath ^[22] |
|-----------------|--|

End point description:

FEV3 (forced expiratory volume in three seconds) is the amount of air which can be forcibly exhaled from the lungs in the first three seconds of a forced exhalation, measured through spirometry testing. A positive change from baseline in FEV3 is considered a favourable outcome. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 12 | |
| Notes: | |
| [22] - 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: Endpoint specific to and only reported for MCTD participants | |

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 0 ^[23] | | |
| Units: liters (L) | | | | |
| arithmetic mean (standard deviation) | 0.460 (± 999) | () | | |

Notes:

[23] - The insufficient sampling scheme did not allow to provide the data.

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Diffusing capacity of the lungs for carbon monoxide (DLCO)

| | |
|-----------------|---|
| End point title | MCTD participants: Diffusing capacity of the lungs for carbon monoxide (DLCO) ^[24] |
|-----------------|---|

End point description:

Diffusing capacity of the lungs for carbon monoxide (DLCO) is a measurement to assess the ability of the lungs to transfer gas from inspired air to the bloodstream. Inhaled carbon monoxide (CO) is used for this test due to its high affinity for hemoglobin. During a ten-second breath-hold, DLCO measures uptake of CO per time per CO pressure. The outcome is presented as percentage of predicted DLCO value. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 24

Notes:

[24] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 1 | 2 | | |
| Units: percentage of predicted DLCO | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 84.0 (± 999) | 95.5 (± 2.12) | | |
| Week 24 (n= 0, 0) | 999 (± 999) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in King's Brief Interstitial Lung Disease (K-BILD)

| | |
|-----------------|--|
| End point title | MCTD participants: Change from baseline in King's Brief Interstitial Lung Disease (K-BILD) ^[25] |
|-----------------|--|

End point description:

The K-BILD questionnaire is a self-administered health-status questionnaire that has been developed in patients with interstitial lung diseases. It consists of 15 items in three domains: breathlessness and activities, psychological factors, and chest symptoms. Total scores range from 0 to 100, with higher scores representing better health status. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12 and 24

Notes:

[25] - 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.

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 1 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 | 3.00 (± 4.243) | -2.00 (± 999) | | |
| Week 8 | 13.00 (± 9.899) | 0.00 (± 999) | | |
| Week 12 (n= 1,0) | 21.00 (± 999) | 999 (± 999) | | |
| Week 24 (n= 1,0) | 58.00 (± 999) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: MCTD participants: Change from baseline in Raynaud's Condition Score (RCS)

| | |
|-----------------|--|
| End point title | MCTD participants: Change from baseline in Raynaud's Condition Score (RCS) ^[26] |
|-----------------|--|

End point description:

The Raynaud's Condition score (RCS) is participant's rating of difficulty considering number of attacks, duration, amount of pain, numbness, or other symptoms caused in the fingers (including painful sores) due to the Raynaud's phenomenon and impact of Raynaud's alone on use of hands every day. An 11-point Likert scale is used to rate the difficulty caused by the condition with 0 = no difficulty and 10 = extreme difficulty. Participants are asked to select the number that best describes their difficulty, with higher score indicating worse condition. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 12 and 24

Notes:

[26] - 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: Endpoint specific to and only reported for MCTD participants

| End point values | MHV370 200mg - MCTD | Placebo - MCTD | | |
|--------------------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 2 | | |
| Units: Score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n= 2,1) | -2.50 (± 3.536) | 1.00 (± 999) | | |
| Week 12 (n= 1,0) | -1.00 (± 999) | 999 (± 999) | | |
| Week 24 (n= 1,0) | -2.00 (± 999) | 999 (± 999) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 199 days.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | MHV370 200 mg b.i.d |
|-----------------------|---------------------|

Reporting group description:

MHV370 200 mg b.i.d

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

| Serious adverse events | MHV370 200 mg b.i.d | Placebo | Total |
|---|---------------------|----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | MHV370 200 mg b.i.d | Placebo | Total |
|---|---------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 14 (92.86%) | 14 / 16 (87.50%) | 27 / 30 (90.00%) |
| Vascular disorders | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| Hypertension subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Vasculitis subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 2 |
| General disorders and administration site conditions Feeling hot subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 2 | 1 / 30 (3.33%) 2 |
| Malaise subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Swelling subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Reproductive system and breast disorders Ovarian cyst subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 2 / 16 (12.50%) 2 | 5 / 30 (16.67%) 5 |
| Cough | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Antinuclear antibody increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Complement factor C3 decreased | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 16 (12.50%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Complement factor C4 decreased | | | |

| | | | |
|--|----------------------|----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Glomerular filtration rate decreased subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Cardiac disorders | | | |
| Extrasystoles subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Sinus bradycardia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 2 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 2 | 1 / 30 (3.33%) 2 |
| Nervous system disorders | | | |
| Sciatica subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Neuralgia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Hypergeusia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Headache subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 6 / 16 (37.50%) 8 | 8 / 30 (26.67%) 10 |
| Facial paralysis | | | |

| | | | |
|---|---------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 1 / 16 (6.25%) 3 | 2 / 30 (6.67%) 4 |
| Blood and lymphatic system disorders | | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 3 / 16 (18.75%) 3 | 3 / 30 (10.00%) 3 |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 3 / 16 (18.75%) 3 | 3 / 30 (10.00%) 3 |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Eye disorders | | | |
| Conjunctival suffusion subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Cataract subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 16 (6.25%) 1 | 1 / 30 (3.33%) 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Abdominal distension | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Parotid gland enlargement | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Paraesthesia oral | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Mouth swelling | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Duodenitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 16 (12.50%) | 3 / 30 (10.00%) |
| occurrences (all) | 2 | 2 | 4 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Abdominal pain upper | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 2 / 16 (12.50%) 2 | 2 / 30 (6.67%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 2 | 1 / 16 (6.25%) 1 | 2 / 30 (6.67%) 3 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Cutaneous vasculitis subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Acne subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Endocrine disorders | | | |
| Thyroid mass subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Vertebral foraminal stenosis subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 1 / 16 (6.25%) 1 | 3 / 30 (10.00%) 3 |
| Infections and infestations | | | |
| COVID-19 subjects affected / exposed occurrences (all) | 4 / 14 (28.57%) 4 | 2 / 16 (12.50%) 2 | 6 / 30 (20.00%) 6 |

| | | | |
|-----------------------------------|-----------------|----------------|-----------------|
| Cystitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Dacryocanaliculitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Helicobacter infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Rash pustular | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 16 (0.00%) | 1 / 30 (3.33%) |
| occurrences (all) | 1 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 16 (6.25%) | 3 / 30 (10.00%) |
| occurrences (all) | 2 | 1 | 3 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 16 (6.25%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 2 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 16 (6.25%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 1 | 2 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|------------------------------------|----------------|-----------------|----------------|
| Metabolism and nutrition disorders | | | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 2 | 2 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 16 (6.25%) | 1 / 30 (3.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 16 (12.50%) | 2 / 30 (6.67%) |
| occurrences (all) | 0 | 3 | 3 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 16 (6.25%) | 2 / 30 (6.67%) |
| occurrences (all) | 1 | 1 | 2 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 25 August 2021 | The reason for this amendment was to update the exclusion criteria and assessment schedule, changed ECG from local to central assessments, SAE reporting, and revised the protocol summary to reflect cardiovascular disease or ECG abnormalities (indicating significant safety risk for the participants) as key exclusion criterion. |
| 29 September 2021 | The reason for this amendment was to update the exclusion criteria, laboratory evaluations, discontinuation from study treatment criteria, and the study stopping rules. |
| 09 May 2022 | The reason for this amendment was to update the discontinuation criteria for those patients that test positive for SARS-CoV-2 based on emergent data. Also, added a secondary efficacy endpoint called 'STAR', and added an interim analysis planned after approximately 50% of SjS participants had completed 24 (and not 12) weeks of treatment to evaluate the efficacy of MHV370. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported