3. SYNOPSIS

<table>
<tr><td rowspan="3">Sponsor/Company:
Shionogi B.V.
Herengracht 464
1017CA Amsterdam,
The Netherlands</td><td>Individual Study Table Referring to Part of the Dossier</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Volume:</td></tr>
<tr><td>Page:</td></tr>
<tr><td>Study Title:</td><td colspan="2">A Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and dose-response of S-337395 in healthy participants challenged with respiratory syncytial virus (RSV)</td></tr>
<tr><td>Protocol Number:</td><td colspan="2">2212T1421</td></tr>
<tr><td>hVIVO Study Number:</td><td colspan="2">JSI-CST-001</td></tr>
<tr><td>IRAS ID:</td><td colspan="2">1008735</td></tr>
<tr><td>Study Phase:</td><td colspan="2">2a</td></tr>
<tr><td>Compound:</td><td colspan="2">S-337395</td></tr>
<tr><td>Challenge Agent:</td><td colspan="2">RSV-A Memphis 37b</td></tr>
<tr><td>Principal Investigator:</td><td colspan="2">Nikolay Veselinski, MD</td></tr>
<tr><td>Number of Study Sites and Countries:</td><td colspan="2">This study was conducted at 1 site that enrolled participants in the United Kingdom (UK).</td></tr>
<tr><td>Publications (reference):</td><td colspan="2">None at the time of this report.</td></tr>
<tr><td>Studied Period:</td><td colspan="2">Study initiation date: 03-April-2024 (first participant first visit)
Study completion date: 07-October-2024 (last participant last visit)</td></tr>
<tr><td colspan="3">Indication: Treatment of RSV infection</td></tr>
<tr><td colspan="3">Rationale:
The purpose of this study was to confirm the antiviral activity and safety of S-337395 in a population inoculated with RSV-A Memphis 37b. In addition, the dose-response of S-337395 was assessed.</td></tr>
<tr><td colspan="3">Objectives and Endpoints:
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<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td colspan="2">Efficacy</td></tr>
<tr><td>• To assess the antiviral activity of S-337395 in healthy adult participants infected with RSV-A Memphis 37b, compared to placebo.</td><td>• Area under the viral load-time curve (VL-AUC) of RSV challenge virus as determined by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) in nasal samples, starting at initial administration of investigational medicinal product (IMP) up to planned discharge.</td></tr>
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Objectives	Endpoints
Secondary	
Efficacy	
• To evaluate the effect of S-337395 in healthy adult participants inoculated with RSV in terms of antiviral effect, compared to placebo, as assessed by: o Viral load-related endpoints.	Additional viral load endpoints relating to antiviral effect included, but were not limited to: • Peak viral load (VLPEAK) of RSV challenge virus as defined by the maximum viral load as determined by qRT-PCR in nasal samples, starting at initial administration of IMP up to planned discharge. • Time (days) to VLPEAK as determined by qRT-PCR measurements in nasal samples, starting at initial administration of IMP. • Time to cessation of virus detection by qRT-PCR (i.e., time [days] to confirmed negative test by qRT-PCR measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure). • Time (days) from VLPEAK to cessation of virus detection by qRT-PCR (i.e., time [days] to confirmed negative test by qRT-PCR measurements in nasal samples starting from the peak measure after initial administration of IMP to first confirmed undetectable assessment after peak measure). • VL-AUC of RSV challenge virus as determined by viral culture on nasal samples, starting at initial administration of IMP up to planned discharge. • VLPEAK of RSV challenge virus as defined by the maximum viral load determined by viral culture measurements in nasal samples, starting at initial administration of IMP up to planned discharge. • Time (days) to VLPEAK as determined by viral culture measurements in nasal samples, starting at initial administration of IMP. • Time to cessation of virus detection by viral culture (i.e., time [days] to confirmed negative test by viral culture measurements in nasal samples starting at initial administration of IMP to first confirmed undetectable assessment after peak measure). • Time (days) from VLPEAK to cessation of virus detection by viral culture (i.e., time [days] to confirmed negative test by viral culture measurements in nasal samples starting from the peak measure after initial administration of IMP to first confirmed undetectable assessment after peak measure).

Objectives	Endpoints
• To evaluate the effect of S-337395 in healthy adult participants inoculated with RSV in terms of antiviral effect, compared to placebo, as assessed by: o Clinical symptom-related endpoints.	Clinical symptom-related endpoints included, but were not limited to: • Area under the curve over time of total clinical symptoms (TSS-AUC) as measured by graded symptom scoring system collected 3 times daily, starting at initial administration of IMP up to planned discharge. • Peak symptoms diary card score: peak total (clinical) symptoms score (TSS) as measured by graded symptom scoring system collected 3 times daily, starting at initial administration of IMP up to planned discharge. • Peak daily symptom score: individual maximum daily sum of symptom score from initial administration of IMP up to planned discharge. • Time (days) to peak symptom score as measured by graded daily symptom scoring system, starting at initial administration of IMP to the time of peak daily symptom score. • Time (days) to symptom resolution as measured by graded daily symptom scoring system, starting at initial administration of IMP. • Time (days) to symptom resolution as measured by graded daily symptom scoring system, starting from the peak measure after initial administration of IMP. • Duration of clinical symptoms: any symptoms, starting at initial administration of IMP up to planned discharge. • Duration of clinical symptoms: grade 2 or higher symptoms, starting at initial administration of IMP up to planned discharge.
• To evaluate the effect of S-337395 on nasal discharge in healthy adult participants inoculated with RSV when compared to placebo.	• Total weight of mucus produced, starting at initial administration of IMP up to planned discharge. • Total number of tissues used by participants, starting at initial administration of IMP up to planned discharge.
Safety	
• To evaluate the safety of multiple orally administered doses of S-337395, when compared to placebo.	• Safety data including, but not limited to, occurrence of adverse events (AEs) from initial administration of IMP up to the Day 28 follow-up.

Objectives	Endpoints
Exploratory*	
Pharmacokinetics	
• To explore the dose-response relationship of S-337395.	Exploratory endpoints related to pharmacokinetics (PK) included, but were not limited to: • After the first and last dose, the following PK parameters were derived: maximum concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$). Only after the last dose, the following PK parameters will be derived: half-life ($t_{1/2}$), elimination rate constant (λ_z), and apparent clearance (CL/F). • PK samples were taken predose to assess trough concentrations (C_{trough}).
• To correlate plasma PK S-337395 levels with changes in viral load and clinical symptoms in S-337395 treated participants compared to placebo.	• Plasma PK correlations with viral load (e.g., qRT-PCR, cell-based infectivity) and symptom scores, e.g., total symptom scores.
Safety	
• To monitor the safety of the challenge virus.	• Occurrence of AEs and serious AEs (SAEs) related to the viral challenge from viral challenge (Day 0) up to the Day 28 follow-up. • Use of concomitant medication from viral challenge (Day 0) up to the Day 28 follow-up.
Viral Resistance	
• To explore viral resistance to S-337395.	• Viral ribonucleic acid (RNA) sequencing could be performed on laboratory-confirmed positive nasal wash samples.
Immunology and Efficacy	
• To explore baseline immunology and response to infection with RSV and response to S-337395 therapy.	• Blood and nasal samples could be used for exploratory assays related to respiratory viral infection and immunology.
• To explore the effect of S-337395 compared to placebo in healthy adult participants inoculated with RSV in terms of antiviral effect assessed by clinical symptom-related endpoints.	• Clinical symptom-related endpoints could be further explored, as measured with either the full 13 or a subset of the 13 symptoms within the graded symptom scoring system. • Patient perception questionnaire results (presence or absence of cold, change in severity of cold) could be compared to other virological and symptomatic endpoints in relation to respiratory viral disease, including but not limited to construct validations.

* Note that exploratory objectives and endpoints were optional and were assessed only if needed; therefore, not all testing was performed and reported.

Methodology:

This was a single-center, randomized, double-blind, placebo-controlled, parallel-group study in healthy adult male and female participants from 18 to 55 years of age, inclusive, utilizing:

- IMP (active): S-337395 powder for oral suspension, dosed once daily for 5 days.
- IMP (placebo): placebo to match S-337395 powder for oral suspension, dosed once daily for 5 days.
- Challenge agent: RSV-A Memphis 37b, intranasal, single dose.

The primary goal of this Phase 2a study was to assess the antiviral activity of S-337395 against RSV in the viral challenge model. In addition, safety, tolerability, and PK of S-337395 were assessed.

Approximately 114 participants were planned to be enrolled in this study, divided over 5 treatment groups:

- Group A: 1 mg S-337395, n=10
- Group B: 10 mg S-337395, n=26
- Group C: 30 mg S-337395, n=26
- Group D: 300 mg S-337395, n=26
- Group E: Placebo, n=26

Group A was used for assessment of dose-response at a subtherapeutic concentration. Groups B, C, D, and E were used for assessment of the antiviral activity of S-337395.

The expected duration of study participation for a participant was approximately 4 months, with the following sequence and duration of study phases:

- **Screening phase**: From Day -90 to Day -2/-1 pre-quarantine admission.
- **Inpatient phase**: Participants were resident in the quarantine unit for approximately 16 days (from Day -2/-1 to Day 13). Procedures included:
  - **Pre-human viral challenge (HVC)**
    - Admission to quarantine unit on Day -2/-1.
    - Signing of study-specific informed consent form (ICF).
    - Baseline assessments were conducted as per Schedule of Events (SoE) up to Day 0, pre-challenge.
  - **HVC**
    - RSV-A Memphis 37b virus inoculation on Day 0.
    - Study assessments were conducted as per SoE on Day 0.
  - **Post-HVC**
    - Randomization to receive S-337395 or matched placebo.
    - Administration of IMP (S-337395/placebo). Each participant received IMP once daily for 5 consecutive days:
      - IMP dosing started on confirmation of RSV infection, i.e., after a positive result by qualitative integrative cycler PCR (qicPCR). The earliest start of IMP dosing was in the evening of Day 2 post-HVC (IMP was initiated 12 hours [±1 hour] post-nasal wash confirmation of infection),

        OR
      - IMP dosing started in the evening of Day 5, if no positive result was obtained by qicPCR by the morning of Day 5.
    - Day 1 onwards and each day – study assessments were conducted as per SoE.
    - Participants were discharged from the quarantine unit on Day 13 (or remained longer at the discretion of the principal investigator [PI]/investigator).
- **Outpatient phase:**
  - Final visit: Day 28 (±3 days).

Number of Participants (Planned and Analyzed):
Planned: 114
Included (randomized): 114
Completed: 113

Main Criteria for Inclusion and Exclusion:
Healthy adult male and female participants aged between 18 to 55 years, inclusive, with a total body weight ≥50 kg and body mass index (BMI) ≥18 kg/m^2 and ≤35 kg/m^2, who were serosuitable for infection with the RSV-A Memphis 37b challenge virus.

Study Intervention:

Investigational medicinal product

- S-337395 powder for oral suspension
  Dose: 1 mg, 10 mg, 30 mg, or 300 mg once daily for 5 days
  Mode of administration: oral
  Batch numbers:

S-337395 Dose Level	Batch Number
1 mg	301790/C/12
10 mg	301790/C/13
30 mg	301790/C/14
300 mg	301790/C/15

- Placebo: placebo to match S-337395 powder for oral suspension
  Dose: not applicable
  Mode of administration: oral
  Batch number: 301790/C/11

Challenge agent

RSV-A Memphis 37b virus
Volume/titer: ~4 $\log_{10}$ plaque-forming units (PFU)
Mode of administration: intranasal

Duration of Study Intervention

6 days (HVC on Day 0 + 5 days of IMP administration). There could be a lag period between HVC on Day 0 and IMP administration; IMP administration was initiated upon confirmation of infection, but no later than the evening of Day 5.

Statistical Analysis:

The primary efficacy analysis was conducted on the intent-to-treat infected (ITT-I) analysis set.

The primary statistical hypothesis was that treatment with S-337395 will show an antiviral effect demonstrated by a significant reduction in VL-AUC of RSV-A Memphis 37b (as determined by qRT-PCR in nasal samples) compared to placebo. This hypothesis was tested for Groups B, C, and D using a 2-sided α level of 0.05, without adjustment. Group A was compared to placebo for exploratory purposes only.

All safety analyses, with the exception of the challenge-emergent AEs (CEAEs), were computed on the safety analysis set. Analysis of CEAEs was performed on the enrolled analysis set. Participants were analyzed in their as-treated group corresponding to what they actually received.

Further details on the efficacy and safety analyses are described in the statistical analysis plan (SAP).

Summary of Results:

Disposition

In total, 114 participants were inoculated with challenge agent (i.e., enrolled) and randomized. One participant (30 mg S-337395) did not complete the inpatient phase (quarantine) as he had to return home due to a family emergency; only the first 2 doses of IMP were administered. This participant was not replaced. All other participants received all doses of IMP and completed the study.

Demographic and Other Baseline Characteristics

There was a difference between the treatment groups with respect to sex; there were more male participants in the placebo, 30 mg S-337395, and 300 mg S-337395 groups than in the 1 mg and 10 mg S-337395 groups. This trend was more pronounced for the ITT-I analysis set. However, this difference is not expected to have impacted the study results.

Exposure

All participants were inoculated with a single dose of challenge agent.

All but 1 participant received the planned dose of placebo or active. In the 30 mg S-337395 group, 1 participant did not complete the inpatient phase (quarantine) and received a total dose of 60 mg S-337395 instead of the planned total dose of 150 mg; he had to return home due to a family emergency and received the first 2 doses only.

Efficacy

Administration of S-337395 (30 mg and 300 mg) once daily for 5 consecutive days was effective in reducing RSV infection as demonstrated by statistically significant reductions in the viral load endpoint VL-AUC (determined by qRT-PCR and viral culture) when compared to placebo.
In addition, statistically significant reductions were observed for mean VLPEAK as determined by qRT-PCR in the 300-mg S-337395 group and mean VLPEAK as determined by viral culture in the 30-mg and 300-mg S-337395 groups when compared to placebo. Over the 10-mg to 300-mg dose range there appears to be a trend toward a lower VL-AUC and VLPEAK with increasing dose.
The reduction in time from baseline to cessation of virus detection by viral culture in the 10-mg and 30-mg S-337395 groups was statistically significant, as was the reduction in time from VLPEAK to cessation of virus detection in the 300-mg S-337395 group when compared to placebo.

The reduction in clinical symptoms as measured by mean TSS-AUC was statistically significant at the highest dose tested (300 mg S-337395) when compared to placebo. Mean peak TSS was statistically significantly reduced in the 30-mg and 300-mg S-337395 groups when compared to placebo.

There were also trends toward reductions in most other viral load- and clinical symptom-related endpoints, but these analyses failed to show statistical significance or were descriptive only.

Safety

Overall, administration of S-337395 (1 mg, 10 mg, 30 mg, and 300 mg) once daily for 5 consecutive days was safe and well tolerated, as was inoculation with the challenge agent.

No SAEs or deaths were reported and none of the AEs led to study discontinuation. No trends in the incidence of AEs were identified. Most AEs were of mild severity; no severe AEs were reported. All AEs were recovered/resolved by the end of the study; 1 AE was recovered/resolved with sequelae.

No dose-dependency was observed for the incidence of TEAEs, and none of the TEAEs was considered to be related to IMP administration.

No clinically significant patterns were observed in clinical laboratory test results (biochemistry, hematology, urinalysis), vital signs, tympanic temperature, ECGs, or physical examination findings. The results were comparable across treatment groups.

Pharmacokinetics

All 88 participants who received S-337395 were included in the PK analysis.

- C_{max}, C_{trough}, and $AUC_{0-\tau}$ on Day 1 after multiple doses of S-337395 300 mg were 1,610 ng/mL, 502 ng/mL, and 22,560 ng·hr /mL, respectively. C_{max}, C_{trough}, and $AUC_{0-\tau}$ on Day 5 after

multiple doses of S-337395 300 mg were 2,620 ng/mL, 972 ng/mL, and 40,710 ng·hr/mL, respectively.

- Median T_{max} on Day 1 after multiple doses of S-337395 at 1, 10, 30, and 300 mg were 6.03, 4.96, 4.96, and 2.90 hours, respectively. Median T_{max} on Day 5 after multiple doses of S-337395 at 1, 10, 30, and 300 mg were 6.86, 3.94, 2.95, and 2.96 hours, respectively.
- Geometric mean $t_{1/2,z}$ on Day 5 after multiple doses of S-337395 at 1, 10, 30, and 300 mg were 16.1 to 16.9 hours.
- C_{max}, C_{trough}, and $AUC_{0-\tau}$ after multiple doses of S-337395 exhibited a moderate to high inter-individual variability (% coefficient of variation [CV] geometric mean ranged from 22.0% to 51.7% on Day 1 and from 29.6% to 66.7% on Day 5).

The PK/pharmacodynamic (PD) analyses were performed using the data for 34 participants in the PK/PD-A analysis population.

- For the percent relative reduction of VL-AUC by qRT-PCR and viral culture, large inter-individual variability in the viral reduction rates were observed at lower C_{24} (i.e., plasma concentration 20 to 28 hours post first dose) while the trends diminished, and higher viral reduction rates were observed at higher C_{24} in the S-337395 C_{24} evaluated in this study. The PK/PD models for the percent relative reduction of VL-AUC by qRT-PCR and viral culture were appropriately established using E_{max} model since the predicted values from the model well described the observed values. The estimated concentration which produces 80% of maximum effect (EC_{80}) of the percent relative reduction of VL-AUC by qRT-PCR was 256 ng/mL.
- The relationship between C_{24} and the time to cessation of virus detection by qRT-PCR tended to be shorter with the increase in C_{24}.

Conclusion:

The results demonstrate that administration of S-337395 (1 mg, 10 mg, 30 mg, and 300 mg) once daily for 5 consecutive days, starting upon confirmation of RSV infection, is safe and well tolerated. In addition, after RSV viral challenge, treatment with S-337395 is generally effective in reducing viral load (as measured by VL-AUC and VLPEAK) and clinical symptoms (as measured by TSS-AUC and peak TSS) at the highest 2 doses tested.

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