CLINICAL STUDY PROTOCOL

A Phase 2 Open-Label Study in Infants with REspiratory Syncytial VIRus Lower RespirAtory Tract Infection, Followed by a DoubLe-blind, Placebo-controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect of RV521 (REVIRAL 1)

Protocol Number:	REVC003
EudraCT Number:	2018-001010-15
CCI [redacted]	[redacted]
Investigational Product:	RV521 (sisunatovir)
Phase:	Phase 2
Sponsor:	ReViral Ltd Stevenage Bioscience Catalyst Gunnels Wood Road Stevenage Hertfordshire SG1 2FX England
Contract Research Organisation:	Syneos Health Corporate Headquarters 1030 Sync Street Morrisville, NC 27560 United States
Protocol Date:	30 Jul 2018
Protocol Version:	Version 1.0
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Protocol Amendment 2:	13 May 2019 (Version 3.0)
Protocol Amendment 3:	15 Jan 2020 (Version 4.0)
Protocol Amendment 4:	01 Mar 2021 (Version 5.0)
Protocol Amendment 5:	31 Jan 2022 (Version 6.0)

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 2 Open-Label Study in Infants with REspiratory Syncytial **VIRus** Lower RespirAtory Tract Infection, Followed by a DoubLe-blind, Placebo-controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect ofRV521(REVIRAL 1)

Protocol Number: REVC003

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

PPD

PPD

Signature

PPD

Date PPD

Contract Research Organisation Signatory

PPD

PPD MD

PPD

PPD

Signature PPD

PPD

Date

2 STUDY PERSONNEL

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3 SYNOPSIS

Protocol Number:

REVC003

Title:

A Phase 2 Open-Label Study in Infants with **RE**spiratory Syncytial **VIR**us Lower Respir**A**tory Tract Infection, Followed by a Doub**L**e-blind, Placebo-controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect of RV52**1** (REVIRAL 1).

Investigational Product:

RV521

Study Centres:

Approximately 75 centres in approximately 15 countries from the Northern and Southern Hemispheres

Phase:

Phase 2

PART A and PART B: Objectives and Endpoints:

Primary Objective	**Primary Endpoints**
To evaluate the safety and tolerability of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalised with Respiratory Syncytial Virus (RSV) lower respiratory tract infection (LRTI)	Safety and tolerability parameters to be assessed will include, but are not limited to: • Adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs (SAEs), and withdrawals due to TEAEs • Physical examinations • Vital sign parameters (ie, systolic and diastolic blood pressure [BP], temperature, respiration rate [RR], heart rate [HR], and pulse oximetry), and changes from baseline in these parameters at predefined time points • Laboratory tests (haematology, chemistry, and urinalysis test results) and changes from baseline in these parameters, at predefined time points • Electrocardiogram (ECG) measurements and changes from baseline in these parameters at predefined time points
Secondary Objectives	**Secondary Endpoints**
To characterise the pharmacokinetics (PK) of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalised with RSV LRTI	Secondary endpoints related to PK will include but are not limited to: • Time to maximum plasma concentration (t_{max}) • Maximum observed plasma concentration(C_{max}) • Area under the plasma concentration time curve from time zero to 12 hours (AUC_{0-12}) • Area under the plasma concentration time curve from time zero to last measurable plasma concentration (AUC_{0-t}) • Terminal half-life ($t_{1/2}$) • Area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) • Predicted plasma clearance • Apparent volume of distribution of the drug after extravascular administration (V/F)

	• Trough concentration at the end of first dosing interval (C_{12}) (data permitting) In addition for Part B: • Accumulation ratio, percent fluctuation • Area under the plasma concentration time curve from time zero to the end of last dosing interval ($AUC_{0\text{-}tau}$) • Average plasma concentration over dosing interval (C_{ave}) • Minimum observed plasma concentration (C_{min}) • Plasma trough concentration (C_{trough}) • Any other relevant parameters
Part B: To evaluate the antiviral effects of RV521 in infants hospitalised with RSV LRTI	Secondary endpoints related to assessment of antiviral activity and efficacy include but are not limited to: • RSV viral load measured in nasopharyngeal swabs by quantitative reverse transcription polymerase chain reaction (RT-qPCR) • RSV viral load measured in nasopharyngeal swabs by cell-based infectivity assay (CBIA)
Part B: Evaluate the effect of RV521 compared to placebo on the clinical course of RSV infection	• Time to resolution of symptoms • Time to improvement evaluated by reduction in severity of symptoms • Reduction in severity of symptoms by RV521, compared to placebo, measured by a composite score over time
Exploratory Objective	**Exploratory Endpoints**
• CCI [redacted]	[redacted]

PART C: Objectives and Endpoints

Primary Objectives for Part C	**Primary Endpoint**
Evaluate the antiviral effects of RV521, compared to placebo, on nasopharyngeal shedding of RSV in infants hospitalised with RSV LRTI	• Time-weighted average change from Baseline to Day 7 in RSV viral load measured in nasopharyngeal swabs by RT-qPCR.
Secondary Objectives for Part C	**Secondary Endpoints**
• To evaluate virologic parameters derived from the RSV viral load as measured in nasopharyngeal swabs	• Virologic parameters derived from the RSV viral load as measured in nasal swabs include but are not limited to: o Change from baseline in viral load (RT-qPCR and CBIA) at each time point o Time to below viral load quantification limit (RT-qPCR and CBIA) o Proportion of subjects with viral load below quantification limit (RT-qPCR and CBIA) at each timepoint throughout the study

• CCI [redacted] • To evaluate the clinical efficacy of multiple oral doses of RV521 in infants hospitalised with RSV LRTI • Evaluate the safety and tolerability of RV521 given as a multiple dose regimen	CCI [redacted] • Time to resolution in RSV-related symptoms • Time to improvement of RSV-related symptoms • Reduction in severity of symptoms by RV521, compared to placebo, measured by a composite score over time • Use of supplemental oxygen, including, but not limited to, duration and maximum level of O_2 provided • Time to normalisation of respiratory rate • Safety of RV521 compared to placebo assessed by incidences of AEs, discontinuations due to AEs, SAEs, and clinically significant changes in clinical laboratory tests
CCI [redacted]	[redacted]

Study Design:

The clinical study consists of 3 parts:

- Part A is an open-label, multicentre, single-dose study in infants hospitalised with RSV LRTI
- Part B is a randomised, double-blind, placebo-controlled, multicentre multiple dose study in infants hospitalised with RSV LRTI
- Part C is a randomised 1:1:1, double-blind, placebo-controlled, multicentre, multiple-dose study comparing two dose levels of RV521 to matching placebo in infants ≥1 months and ≤36 months hospitalised with RSV LRTI.

The number of subjects enrolled in Parts A and B of the study will depend on the safety and PK data from the group of subjects enrolled in specified cohorts and the subsequent recommendation of the Data Safety Monitoring Committee (DSMC). The DSMC will review all available safety and PK data collected from the first 3 subjects and subsequent 3 subjects in Cohort 1 and determine the starting dose for subjects in Cohort 2 (either 2 mg/kg or an adjusted dose based on Cohort 1 safety and PK data).

The DSMC may recommend a dose adjustment (either a reduction or an escalation) and/or regimen adjustment (Part B only) for subsequent subjects because of the observation of an unexpected safety/tolerability profile and/or differences between the observed and predicted exposure resulting from a specified dose of RV521.

Part C will evaluate 111 subjects total (37 per treatment arm) aged ≥ 1 month to ≤ 36 months with an aim to have at least 34 evaluable subjects per treatment group. The primary endpoint will be the time-weighted average change from Baseline to Day 7 in RSV viral load measured in nasopharyngeal swabs by RT-qPCR comparing two dose levels of RV521 vs. placebo. Secondary endpoints will assess the safety, and efficacy of two dose levels of RV521 vs. placebo. Dose levels in Part C will be selected following the analysis of PK data, tolerability and safety from Part B. Two doses (RV521 age group specific high dose and RV521 age group specific low dose) will be selected for inclusion in Part C. The high dose will be selected for each age group to target approximately 90% of subjects achieving the target trough concentration for efficacy (3x EC_{90}), while not exceeding the upper safety limit, based on the paediatric PK model. The low dose will be selected such that the target trough level of 3xEC_{90} is achieved in approximately 75% of the subjects. The high dose may be the highest tolerated dose from Part B, or a higher twice daily dose of RV521, depending on the safety, tolerability and PK data from Part B.

Subjects in Part C will be stratified by age (≥1 to < 6 months of age vs. ≥ 6 months to ≤ 36 months of age) and randomised in a 1:1:1 ratio. Both age strata will be enrolled in parallel. To maintain the double-blind, subjects randomised to placebo will be allocated to low volume (to match the volume associated with the lowest tested dose of RV521) or the higher volume (to match the highest tested dose of RV521).

The DSMC will periodically review the safety and tolerability in Part C in accordance with the DSMC Charter, and may make recommendations about study continuance or dose termination. In the event that a higher dose is selected for evaluation in Part C than was evaluated in Part B, the safety and PK results of the first 9 subjects in each age stratum (3 subjects per arm) will be reviewed in an unblinded manner by the DSMC. The primary focus of this DSMC review will be on the safety and PK profile of the subjects receiving the new higher dose. In the absence of any safety signals in the first 9 subjects in each age stratum, the Safety Physician may determine that continued randomisation of additional subjects is warranted during the DSMC review period. In the event that there is a safety signal of concern, the Safety Physician will make the determination that all randomisation will be halted until the DSMC has completed their review and has recommended that further randomisation may continue. An earlier meeting of the DSMC can be convened, as warranted, and based on the results of the DSMC review, the DSMC may recommend to the Sponsor that a dose of RV521 be terminated. The Sponsor will make the final decision.

Part A (Single dose)

Part A of the study will be conducted across 2 cohorts and will comprise 2 age groups:

- Cohort 1: subjects ≥ 6 months to ≤ 36 months
- Cohort 2: subjects ≥ 1 month to < 6 months

The proposed starting doses of RV521 of 2.5 mg/kg for subjects ≥ 6 months to ≤ 36 months of age (Cohort 1) and 2 mg/kg for subjects ≥ 1 month to < 6 months of age (Cohort 2) are expected to deliver a specified group mean exposure (1× EC_{90} at trough concentration) based on PK modelling and simulation using existing clinical data in healthy adult subjects (CCI and CCI) and nonclinical data. Pharmacokinetic data from groups of 3 subjects in Cohort 1 and Cohort 2 will be reviewed to identify any differences between the observed and predicted exposure resulting from a specified dose of RV521. Safety data will be sent to the DSMC for review prior to any dose adjustment.

Enrolment into Part A of the study will commence with the older subjects (Cohort 1).

Any adjustment(s) of dose level that are required within a cohort will occur in a sequential manner. A maximum of 2 dose adjustments per cohort are planned. Thus, a minimum of 12 subjects (6 per cohort) and a maximum of 24 subjects (12 per cohort) may be enrolled in Part A.

Part B (Multiple Dose)

Part B will be conducted across 3 cohorts (Cohorts 3, 4, and 5) comprising the following age groups:

Cohort 3:	≥ 6 months to ≤ 36 months
Cohort 4:	≥ 1 month to < 6 months
Cohort 5:	≥ 1 month to ≤ 36 months

After review of the safety and PK data from a specific age group enrolled in Part A, the DSMC will determine the dosage and dosing regimen to be used in that age group in Part B, such that the target group mean trough concentration is approximately equivalent to 3× EC_{90}, and approve the start of enrolment in that specified age group, ie, Cohort 3 can start after Cohort 1 (Part A) has been finalised and Cohort 4 can start after Cohort 2 (Part A) has been finalised. It is anticipated that subjects enrolled in Part B of the study will receive RV521 or placebo twice daily (BID), 12 hours apart, for a period of 5 consecutive days (total of 10 doses). However, the dosing regimen may be adjusted depending on the DSMC recommendations.

Groups of 4 subjects will be randomised to receive RV521 or placebo (3:1) in Cohort 3 and Cohort 4, with enrolment occurring in parallel. It is envisioned that data from a group of 4 subjects will be sufficient to confirm the dose exposure relationship for RV521 administered according to a multiple dosing regimen and therefore the DSMC

will review all available safety and PK data collected from the first group of 4 subjects in each cohort. In order to identify the optimum dosage and dosing regimen in each age group, a maximum of 2 dosage/dosing regimen adjustments is assumed in either or both of the Cohorts 3 and 4. Subjects ≥ 6 months to ≤ 36 months of age can be enrolled in Cohort 5 after the completion of Cohort 3 and subjects ≥ 1 month and < 6 months can be enrolled in Cohort 5 after the completion of Cohort 4. Cohort 5 will be opened when either Cohort 3 or 4 is complete. Enrolment in Cohort 5 will continue until 24 evaluable subjects have received RV521 or placebo (2:1). The 4 subjects in the dose group that received the specified dose from each of Cohorts 3 and/or 4 will contribute to this overall total. Thus a minimum of 24 subjects and a maximum of 40 subjects (assuming 2 adjustments per age group) may be enrolled in Part B.

Part C (Multiple Dose, Parallel Group, Cohort 6)

Based on the analysis of the safety, PK, and antiviral data following the completion of Part B, Part C will commence to confirm the antiviral effects of the two dose levels of RV521 vs. placebo. Part C is a double-blind and placebo-controlled study, enrolling 1 cohort (Cohort 6) of up to 111 subjects (≥ 1 month to ≤ 36 months of age). After parent/legal guardian informed consent is obtained, and conditional to satisfactory fulfilment of all inclusion criteria and none of the exclusion criteria subjects will be randomised in a 1:1:1 ratio to receive RV521 at one of two dose levels (RV521 high or low dose) or matching placebo. Subjects will be followed for safety and tolerability, samples will be collected for PK levels, and clinical findings will be collected. Nasopharyngeal swabs will be obtained over the course of the study period to evaluate viral load, presence of other respiratory pathogens and the CCI [redacted].

Number of Subjects:

Approximately 175 subjects (24 subjects in Part A, 40 subjects in Part B, and approximately 111 subjects in Part C will be evaluated. Eligible subjects ranging in age from ≥ 1 month to ≤ 36 months who are hospitalised because of RSV LRTI will be enrolled in the study. It is anticipated that 102 to 126 subjects will receive RV521 (12-24 subjects in Part A, 16-28 in Part B, and approximately 74 in Part C), and 45 to 49 subjects will receive placebo (8-12 subjects in Part B and approximately 37 in Part C). The actual total number of subjects will be dependent upon the number of DSMC-recommended dosage/dosing regimen adjustments in Parts A and B, and whether any doses are dropped from Part C following DSMC recommendation.

Treatment:

RV521, a potent small molecule inhibitor of RSV fusion protein mediated cell-cell fusion, and of RSV infection, is formulated as a dry powder blend of RV521 drug substance with mannitol as excipient. The RV521 dry powder blend will be supplied in capsules containing 10, 20, or 50 mg RV521. The placebo capsules will contain mannitol and microcrystalline cellulose. The IMP will be dispersed in a defined volume of permitted suspending diluent prior to oral administration and dosed on a mg/kg basis. Instructions for opening the capsule(s), and dispersing the contents in a fixed volume of suspending diluent prior to administration will be provided in the Pharmacy Manual.

The proposed starting doses of RV521 for subjects ≥ 6 months to ≤ 36 months and ≥ 1 month to < 6 months of age in Part A were calculated from existing clinical and nonclinical data using PK modelling and simulation. A single dose of RV521 will be administered in Part A.

The proposed dosing regimen for Part B is RV521 or placebo administered BID, 12 hours apart, for a period of 5 consecutive days with a total of 10 doses. However, this is subject to the recommendation of the DSMC.

In Part C, one of two doses of RV521 or placebo will be administered to subjects according to the dose and regimen specified for that age group following completion of Part B/Cohort 5 subjects.

Investigational medicinal product (IMP) administration should occur within 12 hours of randomisation for all subjects across all cohorts, in accordance with their assigned dosage and dosing regimen. The times of completion of feeding prior to dosing and commencement of the first feeding after dosing should be recorded in the subject's source notes.

Study Duration:

Part A: Subjects will participate for up to 8 days, and the visit schedule will include:
Screening Visit (-24 hours to first dose), Dosing Visit 1 (-2 hours pre-dose to 18-24 hours post-dose), Post-dosing Visit 2 (48 hours post-dose), and a Telephone Follow-Up (Day 7).

Part B: Subjects will participate up to 13 days, and the visit schedule will include:
Screening Visit (-24 hours to first dose), Dosing Visit 1, Dosing Visit 2, Dosing Visit 3, Dosing Visit 4, Dosing Visit 5, Follow-Up 40-48 hours Post-Dose 10 (Visit Day 7) and a Telephone Follow-Up (Day 12).

Part C: Subjects will participate for up to 35 days, and the visit schedule will include:
Screening (-24 hours to first dose), Dosing Visits 1-5, Follow-Up 40-48 hours Post-Dose 10 (Visit Day 7) and additional follow-up on Day 14 and Day 34. Inpatient duration will be determined clinically by the PI or other health care provider. Follow-Up days are expected to be on an outpatient basis.

Study Population:

Inclusion criteria:

To be eligible for study entry, subjects must satisfy all of the following criteria at the Screening Visit:

1. Male or female ≥ 1 month and ≤ 36 months of age.
2. Weight ≥ 3.5 kg (Parts A, B and C) but ≤ 18 kg (Part C only).
3. Clinical diagnosis of LRTI defined by
    a. Evidence of respiratory infection by one or both of the following with or without fever:
        i. Rhinitis/coryza
        ii. Cough
            AND
    b. Evidence of LRTI by the presence of one or more of the following:
        i. Increased respiratory rate PLUS other evidence of lower respiratory tract disease (eg, laboratory or radiographic evidence).
        ii. Increased respiratory effort as evidenced by one or more of the following:
            1. Grunting with expiration
            2. Nasal flaring
            3. Retraction: intercostal or subcostal
        iii. Wheezing: audible or on chest auscultation
4. A positive RSV diagnostic test (RSV infection confirmed either according to routine site practice [polymerase chain reaction or diagnostic quick test], or using a [Sponsor-provided] commercial kit).
5. Hospitalised because of RSV LRTI (bronchiolitis or bronchopneumonia).
6. For Part B, symptoms of LRTI must be present for no more than 1 week before the Screening Visit, with the first day of symptoms counting as Day 1.
7. For Part C, symptoms of LRTI must be present for no more than 5 days prior to the Screening Visit, with the first day of symptoms counting as Day 1.
8. Expected to remain in hospital for minimum of 3 days (administration of 6 doses) for Part B only.
9. The parent(s)/legal guardian(s) of the subject have provided written informed consent for the subject to participate.
10. The parent(s)/legal guardian(s) are able and willing to comply with the study protocol.

Exclusion criteria:

Subjects will be excluded from the study if 1 or more of the following criteria are applicable at the Screening Visit:

1. Premature (gestational age less than 37 weeks) AND <1 year of post-natal age.
2. Known to have significant comorbidities, including genetic disorders (eg, trisomy 21); cardiopulmonary diseases (eg, haemodynamically significant congenital heart disease); significant pulmonary disease (eg, bronchopulmonary dysplasia, cystic fibrosis); history of surgery for diaphragmatic hernia; any hereditary or acquired metabolic diseases; haematological or other malignancy; or is known to be HIV positive; or has

evidence of severe neurologic impairment or developmental delay that would limit the ability to administer study drug or evaluate the safety or clinical response to IMP.

3. Current respiratory insufficiency likely to require imminent invasive mechanical ventilation (Part C only).
4. Malformation of the gastrointestinal tract including unresolved pyloric stenosis, history of necrotising enterocolitis, short bowel, or other significant condition that would alter drug absorption or increase the risk of diarrhoea.
5. Any clinically significant electrocardiogram (ECG) abnormalities.
6. Known to be immunocompromised.
7. High probability of asthma (per GINA Guidance 2020) with all of the following:
    a. Symptoms (cough, wheeze, heavy breathing) for > 10 days during previous upper respiratory infections
    b. History of > 3 episodes per year or severe episodes and /or night worsening
    c. Between episodes, child has cough, wheeze, or heavy breathing during play or when laughing
    d. Allergic sensitisation, atopic dermatitis, food allergy, or family history of asthma
8. Suspected of having a clinically significant bacterial infection as indicated by symptoms or laboratory findings consistent with a bacterial infection including but not limited to: elevated white blood cell count, elevated C-reactive protein, chest X-ray consistent with bacterial pneumonia, unstable vital signs, hypotension, or evidence of shock or poor perfusion.
9. Has significant oral and/or maxillofacial malformations that would limit the ability to administer IMP.
10. History of renal failure including renal anomalies likely to be associated with renal insufficiency (eg, clinical conditions of renal dysplasia, polycystic renal disease, renal agenesis).
11. Clinical evidence of hepatic decompensation (eg, hepatic disorder with associated coagulopathy or associated encephalopathy) or significantly elevated liver enzymes (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] >3 × the upper limit of normal).
12. History of epilepsy or seizures. Subjects with a history of febrile seizures will be permitted to enrol.
13. Allergy to test medication or constituents.
14. Known to be concurrently infected with COVID-19 virus (SARS-CoV-2).
15. Requires any prohibited medication/therapy during the course of the study:
    a. Requires inhaled, oral, or IV corticosteroid therapy during the dosing period of the study
    b. Has taken within 21 days before dosing, or requires during the dosing period of the study, any drug that could impact on the PK of the investigational product including potent inhibitors or potent and moderate inducers of CYP P450s (as listed in Appendix 17.3).
    c. Has taken within 21 days before dosing, or requires during the dosing period of the study, any prescription medications, over-the-counter (OTC) medications, herbal remedies or dietary supplements containing [redacted] or the [redacted]-containing products [redacted].
    d. Requires the use of Heliox, leukotriene receptor antagonist (eg, montelukast), exogenous surfactant, or mucolytics during the dosing period of the study.
16. Has received 1 or more doses of palivizumab at any time before Screening or received treatment with antiviral therapy for RSV (eg, ribavirin or intravenous [IV] immunoglobulin) within 3 months before the Screening Visit. **Note**: Subjects eligible for palivizumab treatment or other RSV prophylaxis cannot be included in the study.
17. The subject's parent(s) or legal guardian(s) is a study team member (ie, has direct involvement in this study or other studies under the direction of the Investigator or the study centre) or is a family member of either the Investigator or other team members.
18. Currently participating in any investigational study or at the time of screening, has received an investigational product within 3 months or within 5 half-lives of the investigational product, whichever is longer.
19. Any other reason which in the opinion of the Investigator makes the participant unsuitable for a clinical trial.

Safety and Statistical Analysis:

Because of the exploratory nature of Parts A and B of this study, a formal sample size calculation has not been performed. Twenty-four evaluable subjects enrolled in Part B and receiving RV521 or placebo (2:1) at the same

dose level and according to the same dosing regimen for their specified age range group are expected to be sufficient to assess safety, PK and antiviral activity data.

Estimates for total enrolment into Part C are based on a time-weighted average change in RSV $\log_{10}$ viral load from baseline to day 7 in the placebo group of -1.5 $\log_{10}$ vp/ml, with a standard deviation of 1.25. A sample size of 37 per group (total 111 subjects randomised 1:1:1; 2 dose levels of RV521 vs placebo) will provide 90% power to detect at least 1 $\log_{10}$ decrease in the RV521 groups using a 2-sided significance level of 0.05 and assuming a drop out rate of 10%.

Analysis Populations

All safety data analyses will be based on the Safety Population, defined as all subjects who received a single dose (Part A) or any part of any multiple dosing regimen (Parts B and C) of IMP (RV521 or placebo).

The PK population will be defined as all subjects who received RV521 and have at least 1 post-dose PK concentration measured in Parts A, B, or C.

The mITT Population defined in Part A as all subjects enrolled in the study who have an RT-qPCR viral load measurement and/or CBIA, if available, for at least 1 time point including baseline: pre-dose at Dosing Visit 1. In Part B the mITT population will include all subjects who received at least one dose of IMP (RV521 or placebo) and have a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during blind data review. Potential inclusion of subjects who have not completed at least 6 doses of IMP will be decided by the project team during the blind data review meeting. Subjects will be analysed as to their randomised treatment. The mITT population for Part C will include all subjects who receive at least one dose of the study treatments and have a pre-treatment positive RSV confirmed by the central laboratory.

Evaluation of Safety: For laboratory tests, ECG measures, and vital signs parameters, baseline will be defined as the last non-missing result before the first dose of IMP. Results at each visit will be summarised using the statistics: n (number of observations), mean, standard deviation (SD), median, minimum and maximum. In addition, change from baseline for all safety parameters will also be summarised by post-baseline visits.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Summary tables of AEs will be based on TEAEs, defined as events starting, or worsening, after the first dose of IMP. Summaries by MedDRA System Organ Class (SOC) and Preferred Term will be provided for all TEAEs, all treatment-related TEAEs (with causality assessed as possibly, probably, or definitively related to IMP), all serious TEAEs and all TEAEs leading to early discontinuation from the study. Summary tables by maximum severity and maximum relationship will be presented.

Clinical:

RSV-related signs and symptoms will be summarised by duration (number [%] of subjects analysed, mean, median, SD, minimum, maximum). In addition, signs and symptoms will be summarised by highest level of severity by treatment group. Also, change from baseline will also be summarised for post-baseline visits. Baseline will be defined as the last non-missing result before the first dose of IMP.

RSV-related signs and symptoms will include, but are not limited to: respiratory rate, heart rate, wheezing retractions.

For Parts B and C:

Individual RSV symptoms will be summarised by frequency at each time point by treatment assignment. Individual RSV-related symptoms will be summarised, for subjects reporting a symptom at study start, for time to resolution (mean, median, SD, minimum and maximum times).

Time to improvement will be calculated for RSV-related signs and symptoms that are classified as moderate or severe during the course of the study and will be defined as the time from randomisation until no longer present (absent or mild).

The Overall Time to Improvement will be defined as the time from randomisation to the time that all RSV-related signs and symptoms are mild or absent. The overall time to improvement will be summarised for each treatment group by mean, median, SD, minimum and maximum and 95% confidence intervals.

Overall Time to Resolution will be defined as the time of randomisation to the time that all RSV-related signs and

symptoms are absent. The overall time to resolution will be summarised for each treatment group by mean, median, SD, minimum and maximum and 95% confidence intervals.

Treatment groups will be compared for differences in overall severity assessed by the composite symptom score on each day whilst hospitalised and at follow-up visits.

Other analyses may include but are not limited to duration of supplemental oxygen, CCI [redacted].

Pharmacokinetics

Pharmacokinetic analysis will include listings and summaries of PK concentrations by time point, derived PK parameters, and analysis of relationship with dose and body weight.

Pharmacodynamics analysis will include listing of results of viral load with summary statistics by dose level and time point; CCI [redacted].

Pharmacodynamic parameters, including viral load, DAVG, and any other PD parameters which are derived, will be summarised by treatment (dose level). For Parts B and C, comparisons will be made between RV521 and placebo using analysis of covariance models. Data will be log transformed as appropriate. CCI [redacted]

Virology

For Parts B and C: viral load (determined from nasopharyngeal swabs by RT-qPCR) will be analysed using log transformed data. The time-weighted average change in nasopharyngeal RSV viral load will be calculated from baseline (Day of Randomisation to Day 7) and compared across treatment groups.

4 TABLE OF CONTENTS

4.1 List of In-Text Tables

4.2 List of In-Text Figures

5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-12}	area under the plasma concentration-time curve from zero to 12 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from zero to the last measurable concentration
AUC_{0-tau}	area under the plasma concentration-time curve from zero to the end of last dosing interval
bid	two times per day
BP	blood pressure
C_{12}	trough concentration at the end of first dosing interval
C_{ave}	average plasma concentration over dosing interval
CBIA	cell-based infectivity assay
CL	plasma clearance
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma trough concentration
DSMC	Data Safety Monitoring Committee
EC	effective concentration
EC_{90}	90% of the effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBP cyclodextrin	hydroxypropyl-ß-cyclodextrin
HR	heart rate
IB	Investigator's Brochure
IC_{50}	inhibitor concentration that decreases the biotransformation of a substrate at a single, specified concentration by 50%
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IV	Intravenous
LRTI	lower respiratory tract infection
MCH	mean cell haemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PCR	polymerase chain reaction
PD	Pharmacodynamics

CCI	[redacted]
PK	Pharmacokinetics
PR	pulse rate
QTcF	QT Interval by Fridericia's Formula
RR	respiration rate
RSI	reference safety information
RSV	respiratory syncytial virus
RT-qPCR	reverse transcriptase quantitative polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SpO_2	Pulse Oximeter Oxygen Saturation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
V/F	apparent volume of distribution of the drug after extravascular administration
WHO	World Health Organisation

6 INTRODUCTION

6.1 Disease and Indication

Respiratory syncytial virus (RSV), a member of the Pneumoviridae family, is a significant pathogen of the very young, the immunocompromised, and the elderly (Simões, 2015). It is highly infectious and is transmitted through respiratory secretions via close contact with infected individuals, through droplets or through contaminated surfaces (Collins and Karron, 2013). Respiratory syncytial virus is an enveloped virus with a negative single strand ribonucleic acid (RNA) genome that encodes for 11 proteins, including 3 surface glycoproteins (F, G, and SH). There are 2 major serotypes, A and B, that cause similar disease and although they may co-circulate, 1 type usually predominates in alternate years.

By 1 year of age, 60 to 70% of children have been infected with RSV, of whom 2 to 3% will be hospitalised. Virtually all children will have been infected by the age of 2 years (Hall, 2009). In 2015, RSV was estimated to cause 33.1 million cases of acute respiratory illness in children < 5 years of age globally, resulting in 2.7-3.8 million hospital admissions and 48,000 to 74,500 deaths (Shi, 2017; Scheltema, 2017). The majority of children with RSV infection develop upper respiratory tract disease, but 20 to 30% go on to develop bronchiolitis or pneumonia. General practitioner visits and hospitalisation due to RSV infection are a major and significant burden on health care providers and hospitals during RSV outbreaks (Taylor, 2016). There is growing evidence that hospitalised children with RSV disease have higher nasal viral titres than age-matched controls with less severe disease, suggesting a potential opportunity to intervene with an effective antiviral agent (DeVincenzo, 2005; El Saleeby, 2011). There is evidence to suggest that RSV bronchiolitis may create a long-term risk for the development of asthma (Regnier, 2013).

The RSV epidemic is highly predictable year after year. In the northern hemisphere, in general, the virus appears in October, the epidemic peaks early in January and ends in April. The virus then appears in the Southern hemisphere and causes a similar epidemic during the winter season. In the tropics, the virus is present throughout the year (Simões, 2015). Consequently, RSV is a worldwide issue. The burden of illness and mortality due to RSV is highest in children in the developing world.

Very limited management options for RSV infection and disease currently exist. There are only 2 approved therapeutic agents for RSV. The first, ribavirin, a nucleoside analogue has restricted clinical use due to limited antiviral potency, inherent toxicity, and teratogenic potential. The other approved agent is the prophylactic monoclonal antibody (paluvizimab), which interacts with the F glycoprotein of the virus, and has gained widespread use to protect very premature babies in developed countries. However, the antibody must be given throughout the winter season, and the cost of therapy, about 5000 USD per infant for the winter season, limits wider uptake.

RV521 is being developed as a highly potent, selective, orally available agent to treat RSV infection and disease. The primary target populations for RV521 are infants and small children, the immunocompromised, the elderly, and patients with compromised respiratory (chronic obstructive airways disease) or cardiovascular (congestive heart disease) systems.

6.2 RV521 Mechanism of Action

RV521 is a potent inhibitor of RSV F protein mediated cell-to-cell fusion. The RSV F protein is essential for the entry of the virus to the host cell. Cell surface expression of the F protein also causes cell-to-cell fusion, leading to the giant syncytia characteristic of RSV infection.

CCI [redacted]

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6.5 Rationale for the Study

As described, there remains a large unmet medical need for an effective therapy for RSV infection and disease. The RV521 preclinical profile, as well as the safety and tolerability data from the first human dosing studies, provide a strong rationale for the clinical development of RV521. Study REVC003 is part of the Paediatric Investigational Plan, and is a 3-part, Phase 2 study in infants hospitalised with RSV lower respiratory tract infection (LRTI) consisting of an initial open-label period (Part A, single dose), followed by a randomised, double-blind, placebo-controlled Part B (multiple dose), to evaluate the safety, tolerability, pharmacokinetics (PK), and antiviral effect of RV521. The safety, tolerability, PK, antiviral and clinical effect of RV521 will be further explored in Part C (multiple dose).

6.6 Potential Risks and Benefits for Study Participants

Due to its mechanism of action, RV521 is an antiviral agent that targets the RSV F (fusion) protein on the surface of the viral envelope and exerts antiviral activity against RSV by inhibiting viral entry into host cells and preventing F protein induced cell-cell fusion. In this way, F protein inhibition may reduce both viral replication and pathology, reducing the severity of the RSV LRTI. In the clinical studies conducted to date, RV521 had a good safety profile. Nausea, diarrhoea, abdominal pain, and vomiting occurred in clinical studies of RV521, and are considered expected toxicities, clinically. Investigators should use clinical judgement in treating subjects with these events.

For more details, please refer to the currently approved version of the IB for RV521.

7 STUDY OBJECTIVES

7.1 PART A and PART B

7.1.1 Primary Objective

Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalised with RSV LRTI	Safety and tolerability parameters to be assessed will include, but are not limited to: • AEs, TEAEs, SAEs, and withdrawals due to TEAEs • Physical examinations • Vital sign parameters (ie, systolic and diastolic BP, temperature, RR, HR, and pulse oximetry), and changes from baseline in these parameters at predefined time points • Laboratory tests (haematology, chemistry, and urinalysis test results) and changes from baseline in these parameters, at predefined time points • ECG measurements and changes from baseline in these parameters at predefined time points

7.1.2 Secondary Objectives

Secondary Objectives	Secondary Endpoints
To characterise the PK of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalised with RSV LRTI	Secondary endpoints related to PK will include but are not limited to: • Time to maximum plasma concentration (tmax) • Maximum observed plasma concentration(Cmax) • Area under the plasma concentration time curve from time zero to 12 hours (AUC0-12) • Area under the plasma concentration time curve from time zero to last measurable plasma concentration (AUC0-t) • Terminal half-life (t1/2) • Area under the plasma concentration time curve from time zero to infinity (AUC0-∞) • Predicted plasma clearance • Apparent volume of distribution of the drug after extravascular administration (V/F) • Trough concentration at the end of first dosing interval (C12) (data permitting) In addition for Part B: • Accumulation ratio, percent fluctuation • Area under the plasma concentration time curve from time zero to the end of last dosing interval (AUC0-tau) • Average plasma concentration over dosing interval (Cave) • Minimum observed plasma concentration (Cmin) • Plasma trough concentration (Ctrough) • Any other relevant parameters

Secondary Objectives	Secondary Endpoints
Part B: To evaluate the antiviral effects of RV521 in infants hospitalised with RSV LRTI	Secondary endpoints related to assessment of antiviral activity and efficacy include but are not limited to: • RSV viral load measured in nasopharyngeal swabs by RT-qPCR • RSV viral load measured in nasopharyngeal swabs by CBIA
Part B: Evaluate the effect of RV521 compared to placebo on the clinical course of RSV infection	• Time to resolution of symptoms • Time to improvement evaluated by reduction in severity of symptoms • Reduction in severity of symptoms by RV521, compared to placebo, measured by a composite score over time

7.1.3 Exploratory Objective

Exploratory Objective	Exploratory Endpoint
• CCI [redacted]	[redacted]

7.2 PART C: Objectives and Endpoints

Primary Objectives for Part C	Primary Endpoint
• Evaluate the antiviral effects of RV521, compared to placebo, on nasopharyngeal shedding of RSV in infants hospitalised with RSV LRTI	• Time-weighted average change from Baseline to Day 7 in RSV viral load measured in nasopharyngeal swabs by RT-qPCR.
Secondary Objectives for Part C	Secondary Endpoints
• To evaluate virologic parameters derived from the RSV viral load as measured in nasopharyngeal swabs • CCI [redacted]	• Virologic parameters derived from the RSV viral load as measured in nasal swabs include but are not limited to: o Change from baseline in viral load (RT-qPCR and CBIA) at each time point o Time to below viral load quantification limit (RT-qPCR and CBIA) o Proportion of subjects with viral load below quantification limit (RT-qPCR and CBIA) at each timepoint throughout the study • CCI [redacted]

• To evaluate the clinical efficacy of multiple oral doses of RV521 in infants hospitalised with RSV LRTI	• Time to resolution in RSV-related symptoms • Time to improvement of RSV-related symptoms • Reduction in severity of symptoms by RV521, compared to placebo, measured by a composite score over time • Use of supplementary oxygen, including, but not limited to, duration and maximum level of O_2 provided • Time to normalisation of respiratory rate
• Evaluate the safety and tolerability of RV521 given as a multiple dose regimen	• Safety of RV521 compared to placebo assessed by incidences of AEs, discontinuations due to AEs, SAEs, and clinically significant changes in laboratory tests
Exploratory Endpoints (Part C)	[redacted]

8 INVESTIGATIONAL PLAN

8.1 Schedule of Assessments

The schedule of planned study assessments for Part A is shown in Table 1, in Table 2 for Part B, and in Table 3a inpatients and Table 3b outpatients for Part C. The nasopharyngeal swab sampling schedule is shown in Table 4, and the PK sampling schedule is shown in Table 5.

Note: For Parts B and C, if the DSMC recommends a regimen adjustment, eg, once-daily dosing rather than twice-daily dosing, all study assessments, including nasopharyngeal swab and PK sampling schedules will occur as shown in Table 4 and Table 5. In the event of once daily dosing, pre and post-dose PK and nasopharyngeal swab time points related to Dose 6 will be taken at Dose 3 instead.

Table 1. Schedule of Assessments for Part A, Open-Label Part of the Study

Assessment	Screening	Treatment Phase							Post Treatment Phase		
	Screening Visit	Dosing Visit 1							Post-Dosing Visit 2		Telephone Follow-Up Visit
Time Relative to Dose	-24 h to First Dose	-2 h Pre-Dose	0 h Dose	1-2 h Post-Dose	4-5 h Post-Dose	6-8 h Post-Dose	12 h Post-Dose	18-24 h Post-Dose	36 h Post-Dose	48 h Post-Dose	Day 7 Post-Dose
Written Informed Consent[a]	X										
RSV Rapid Diagnostic Test	X										
Inclusion / Exclusion Criteria	X	X									
Demographics[b]	X										
Medical History	X										
Prior Medication Review	X										
Physical Examination[c]	X	X						X		X	
Hydration Status[d]	X	X						X		X	
Body Weight / Length / Head Circumference	X									X	
Vital Signs[e]	X	X			X		X	X		X	
Pulse Oximetry on room air[f]	X	X					X	X		X	
Record Supplemental O_2 use[g]	X	X					X	X		X	
12-Lead ECG[h]	X	X[i]			X			X		X	
RSV Clinical Scoring System[j]	X	X						X		X	
Safety Laboratory Tests (Clinical Chemistry and Haematology)[k]	X									X	
Urinalysis	X									X	
Pharmacokinetics Blood[l]				X	X	X	X[m]	X			
Study Medication Administration[n]			X								
Nasopharyngeal Swab[o]		X					X[p]	X	X[p]	X	
Concomitant Medication Review	X	X	X		X	X	X	X		X	X
Adverse Events Review	X	X	X		X	X	X	X		X	X

Footnotes appear on next page.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; h = hours; IMP = investigational medicinal product; PK = pharmacokinetic; RSV = respiratory syncytial virus.**Note: All procedures and assessments are presented with the Dosing Visit at which they should be conducted. The actual day(s) on which the Dosing Visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1.**

[a] Written informed consent includes the consent for participating in Part A of the study and the written informed consent for the optional Sponsor-provided commercial RSV test.

[b] Demographic data to be collected: date of birth, gender, race, and ethnicity.

[c] Physical examination may also include a symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions (Section 10.1.3.8).

[d] Refer to Appendix 17.5 for the Dehydration Status Evaluation.

[e] Vital signs include body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate, and should be conducted before PK and nasopharyngeal swab samples for the respective time points are taken.

[f] Pulse oximetry to be recorded on room air (if deemed safe by PI or health care provider)

[g] Record supplemental oxygen use

[h] 12-Lead ECG to be performed using the centrally provided ECG machine and before PK and nasopharyngeal swab samples are taken.

[I] The 12-Lead ECG should only be performed using the centrally provided ECG machine at -2 h Pre-Dose, if the centrally provided ECG machine was not used at Screening.

[j] Refer to Appendix 17.1 for the RSV Clinical Scoring System.

[k] At Screening, the AST/ALT values should be obtained from the local laboratory. A blood sample will still need to be sent to the Central laboratory.

[l] The actual day for taking each PK sample is dependent on the time when IMP is administered on Dosing Visit 1 (Day 1) (morning versus afternoon versus evening); eg, if the subject received their first dose of IMP at 22:00 on Day 1, the post-dose samples due to be taken at 4-5 h, 6-8 h, 12 h, and 18-24 h would be taken on Day 2 from 02:00 to 03:00, 04:00 to 06:00, 10:00, and 16:00 to 22:00, respectively (Table 5).

[m] The 12 hour PK sampling window is 30 minutes (Table 5).

[n] The times of the prior feeding and first feeding after dosing should be recorded.

[o] See Table 4 for nasopharyngeal swab sample schedule.

[p] Denote optional nasopharyngeal swab samples.

Table 2. Schedule of Assessments for Part B, Double-Blind, Placebo-Controlled Part of the Study

Assessment	**Screening**	**Treatment Phase**													**Post-Treatment Phase**	
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3			Dosing Visit 4		Dosing Visit 5		Follow up	
		Dose 1			Dose 2	Dose 3	Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9	Dose 10	Visit Day 7	TFU
Time Relative to Dose	-24 to first dose	-2h to 0	0 h	+1-2h Or +4-5h Or +6-8h					0 h	+1-2h Or +4-5 h Or +6-8h				Last Dose	+40-48h Post-Dose 10	Day 12
Written Informed Consent[a]	X															
RSV Rapid Diagnostic Test	X[r]															
Inclusion / Exclusion Criteria	X	X[s]														
Demographics[b]	X															
Medical History	X															
Prior Medication Review	X															
Physical Examination[c]	X	X[s]													X	
Hydration Status[d]	X	X[s]				X		X			X*		X*		X	
Body Weight / Length / Head Circumference	X														X	
Vital Signs[e]	X	X[s]	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X	
12-Lead ECG[f]	X			X		X		X		X		X*		X*	X	
RSV Clinical Scoring System[g]	X	X[s]				X		X			X*		X*		X	
Record RSV Signs and Symptoms[h]	X	X[s]			X	X	X	X	X		X*	X*	X*	X*	X	
Record Supplemental O_2		X			X	X	X	X	X		X*	X*	X*	X*		

Assessment	**Screening**	**Treatment Phase**													**Post-Treatment Phase**	
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3			Dosing Visit 4		Dosing Visit 5		Follow up	
		Dose 1			Dose 2	Dose 3	Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9	Dose 10	Visit Day 7	TFU
Time Relative to Dose	-24 to first dose	-2h to 0	0 h	+1-2h Or +4-5h Or +6-8h					0 h	+1-2h Or +4-5 h Or +6-8h				Last Dose	+40-48h Post-Dose 10	Day 12
Pulse Oximetry on Room Air		X			X	X	X	X	X		X*	X*	X*	X*	X	
Adapted ReSVinet Scale for Parental Use[i]	X														X	
Safety Laboratory Tests (Clinical Chemistry and Haematology) [j]	X														X[t]	
Urinalysis	X														X[t]	
Randomisation for Eligible Subjects		X														
Pharmacokinetics Blood Sample[k]				X[l]	X[m]				X	X[l]	X[m]				X	
Nasopharyngeal Swab[n]		X			X[o]	X	X[o]	X	X		X*[p]	X*[o]	X*	X*[o]	X	
Concomitant Medication Review	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Review	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Administration[q]			X		X	X	X	X	X		X	X	X	X		

Footnotes appear on next page.

Abbreviations: ECG = electrocardiogram; h = hours; PK = pharmacokinetic; RSV = respiratory syncytial virus; TFU = Telephone Follow-up Visit.

Notes: All procedures and assessments are presented against the Dosing Visit at which they should be conducted. The actual day(s) on which the visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1. The Follow-up +40-48 h Post-Dose 10 on Visit Day 7 could therefore occur on Study Days 7 or 8, depending on when the subject received his or her first dose of IMP. Observations (SpO2, viral signs, inspection of RSV symptoms) should precede any procedures that manipulate the subject (physical examination, nasopharyngeal swabs, PK sampling). For the physical examination, listen to the lungs first. In any event, the order should be consistent for all the assessment days.

[a] Written informed consent includes the consent for participating in Part B of the study and the written informed consent for the optional Sponsor-provided commercial RSV test.

[b] Demographic data to be collected: date of birth, gender, race, and ethnicity.

[c] Physical examination may also include a symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions (Section 10.1.3.8). For days when IMP is administered, physical examination should be conducted before a dose of IMP is administered.

[d] Refer to Appendix 17.5 for the Dehydration Status Evaluation.

[e] Vital signs include body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and should be conducted before PK and nasopharyngeal swab samples, for the respective time points, are taken. For the days without PK and nasopharyngeal swab samples, vital signs should be taken before a dose of IMP is administered.

[f] 12-Lead ECG to be performed using the centrally provided ECG machine and before PK and nasopharyngeal swab samples are taken. For days when IMP is administered ECG should be performed before a dose of IMP is administered

[g] Refer to Appendix 17.1 for the RSV Clinical Scoring System. Note: this assessment is to be done only when subject is hospitalised and at follow-up.

[h] Refer to Appendix 17.4 for RSV signs and Symptoms

[i] Refer to Appendix 17.2 for the Adapted version of ReSVinet scale for parental use.

[j] At Screening, the AST/ALT values should be obtained from the local laboratory. A blood sample will still need to be sent to the Central laboratory.

[k] The actual day for taking each PK sample is dependent on the time when IMP is administered on Visit 1 (Day 1) (morning versus afternoon versus evening); eg, if the subject received their first dose of IMP at 22:00 on Day 1, the post-dose samples due to be taken at 4-5 h, 6-8 h, 12 h, and 18-24 h would be taken on Day 2 from 02:00 to 03:00, 04:00 to 06:00, 10:00, and 16:00 to 22:00, respectively (Table 5).

[l] These PK samples will be defined after PK Analysis of Part A. One of those three samples will be requested, the other two will not be required (Table 5).

[m] The 12 hour PK sampling window is 30 minutes (Table 5).

[n] See Table 4 for nasopharyngeal swab sample schedule.

[o] Denote optional nasopharyngeal swab samples.

[p] If the subject is discharged from hospital, a nasopharyngeal swab sample should be obtained prior to discharge if the parents/legal guardians are unlikely to return for the next visit. Note: this sample is not required if the previous sample was taken less than 12 hours before the subject is discharged (Table 4).

[q] The times of the prior feeding and first feeding after dosing should be recorded. IMP should be administered every 12 hours or as dosing regimen recommended by the Data Safety Monitoring Committee with a time window of ± 30 minutes.

[r] All the screening assessments (except the RSV Rapid Diagnostic Test) should be completed within 24 hours before Dose 1. A positive RSV Rapid Diagnostic Test result is required on a sample collected within 48 hours before Dose 1.

[s] It is not necessary to repeat the assessment for the -2h to 0h Pre-Dose 1 timepoint, if the assessment was carried out for screening purposes within the 2h Pre-Dose 1. However, if the screening assessments were carried out >2 h prior to Dose 1 for screening purposes (i.e. within the first 22 hours of the screening window), the assessment must be repeated between -2h to 0h Pre-Dose 1.

[t] Allowed time window on the end of treatment safety bloods and urinalysis is +/- 2 days. Should a subject be discharged after Dose 10, the safety blood sample should be obtained prior to discharge, particularly if the parents/legal guardians are unlikely to return for the next visit.

* Procedure to be done if subject is in the hospital.

Table 3a. Schedule of Assessments for Part C for subjects hospitalised for a minimum of 3 Dosing Visits

Assessment	Screening	Treatment Phase													Post-Treatment Phase		
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3			Dosing Visit 4		Dosing Visit 5		Follow Up		
		Dose 1			Dose 2	Dose 3	Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9	Dose 10	Visit Day 7	Visit Day 14±1 Day	Visit Day 34±1 Day
Time Relative to Dose	-24 to first dose	-2 h to 0 h	0 h	+4-5 h Post-Dose[n]					0 h	+4-5 h Post-Dose[n]				Last Dose	+40-48 h Post-Dose 10	Day 14	Day 34
Written Informed Consent[a]	X																
Inclusion / Exclusion Criteria	X	X[t]															
RSV Rapid Diagnostic Test	X[s]																
Demographics[b]	X																
Medical History	X																
Prior Medication Review	X																
Physical Examination[c]	X	X[t]													X		
Hydration Status[d]	X	X[t]				X		X			X*		X*		X		
Body Weight / Length / Head Circumference	X														X	X	X
Vital Signs[e]	X	X[t]		X	X	X	X	X	X	X	X*	X*	X*	X*	X	X	X
12-Lead ECG[f]	X			X		X		X		X		X*		X*	X		
ReSVinet Score for Clinicians[g]	X	X[t]				X		X			X*		X*		X	X	X
Record RSV Signs and Symptoms[h]	X	X[t]			X	X	X	X	X		X*	X*	X*	X*	X	X	X
Record Supplemental O_2		X			X	X	X	X	X		X*	X*	X*	X*			

Assessment	Screening	Treatment Phase													Post-Treatment Phase		
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3			Dosing Visit 4		Dosing Visit 5		Follow Up		
		Dose 1			Dose 2	Dose 3	Dose 4	Dose 5	Dose 6		Dose 7	Dose 8	Dose 9	Dose 10	Visit Day 7	Visit Day 14±1 Day	Visit Day 34±1 Day
Time Relative to Dose	-24 to first dose	-2 h to 0 h	0 h	+4-5 h Post-Dose[n]					0 h	+4-5 h Post-Dose[n]				Last Dose	+40-48 h Post-Dose 10	Day 14	Day 34
Pulse Oximetry on Room Air		X			X	X	X	X	X		X*	X*	X*	X*			
Adapted ReSVinet Scale for Parental Use[i]	X					X		X			X		X		X	X	X
Safety Laboratory Tests (Clinical Chemistry, and Haematology)[j]	X														X[u]		
Urinalysis	X														X[u]		
Randomisation for Eligible Subjects		X															
Pharmacokinetics Blood Sample[k]				X[l,n]	X[l]				X[l,m,]	X[l,m,n]	X[l]				X[l,m]		
Nasopharyngeal Swab[o]		X			X[p]	X	X[p]	X	X		X[q]*	X[p]*	X*	X[p]*	X	X	X
Concomitant Medication Review	X	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Review	X	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Administration[r]			X		X	X	X	X	X		X	X	X	X			

Footnotes appear on next page.

Abbreviations: ECG = electrocardiogram; h = hours; PK = pharmacokinetic; RSV = respiratory syncytial virus.

Notes: All procedures and assessments are presented against the Dosing Visit at which they should be conducted. The actual day(s) on which the visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1. The Follow-up +40–- 48 h Post-Dose 10 on Visit Day 7 could therefore occur on Study Day 7 or 8, depending on when the subject received his or her first dose of IMP. Observations (SpO2, viral signs, inspection of RSV symptoms) should precede any procedures that manipulate the subject (physical examination, nasopharyngeal swabs, PK sampling). For the physical examination, listen to the lungs first. In any event, the order should be consistent for all the assessment days.

[a] Written informed consent includes the consent for participating in Part C of the study and the written informed consent for the optional Sponsor-provided commercial RSV test.

[b] Demographic data to be collected: date of birth, gender, race, and ethnicity.

[c] Physical examination may also include a symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions (Section 10.1.3.8). For days when IMP is administered, physical examination should be conducted before a dose of IMP is administered.

[d] Refer to Appendix 17.5 for the Dehydration Status Evaluation.

[e] Vital signs include body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and should be conducted before PK and nasopharyngeal swab samples, for the respective time points, are taken. For the days without PK and nasopharyngeal swab samples, vital signs should be taken before a dose of IMP is administered.

[f] 12-Lead ECG to be performed using the centrally provided ECG machine and before PK and nasopharyngeal swab samples are taken. For days when IMP is administered ECG should be performed before a dose of IMP is administered

[g] Refer to Appendix 17.6 for the ReSVinet score for clinicians. Note: this assessment is to be done only when subject is hospitalised and at follow-up visits.

[h] Refer to Appendix 17.4 for RSV signs and Symptoms

[i] Refer to Appendix 17.2 for the Adapted version of ReSVinet scale for parental use. Upon discharge parents/caregivers are to complete at home.

[j] At Screening, the AST/ALT values should be obtained from the local laboratory. A blood sample will still need to be sent to the Central laboratory.

[k] The actual day for taking each PK sample is dependent on the time when IMP is administered on Visit 1 (Day 1) (morning versus afternoon versus evening); eg, if the subject received their first dose of IMP at 22:00 on Day 1, the post-dose samples due to be taken at 4-5 h, 6-8 h, 12 h and 18-24 h would be taken on Day 2 from 02:00 to 03:00, 04:00 to 06:00, 10:00, and 16:00 to 22:00, respectively (Table 5).

[l] Note: If the PK profile for a dose to be evaluated in Part C was not evaluated in Part B, a total of 6 PK samples will be taken for the first 9 subjects (3 per arm) in each age stratum. The DSMC will review the PK data profiles and recommend whether these PK samples are to be taken for subsequently enrolled subjects.

[m] If the PK profile for a dose to be evaluated in Part C was evaluated in Part B, only 3 PK samples will be drawn: Pre-Dose 6, Post Dose 6 sample (+4-5 h), and the sample on Visit Day 7.

[n] The timing of the Post-Dose PK samples and assessments in Part C will be 4-5 h Post-Dose. Please refer to Table 5 for PK sample schedule.

[o] See Table 4 for nasopharyngeal swab sample schedule.

[p] Denotes optional nasopharyngeal swab samples.

[q] If the subject is discharged from hospital, a nasopharyngeal swab sample should be obtained prior to discharge if the parents/legal guardians are unlikely to return for the next visit. Note: this sample is not required if the previous sample was taken less than 12 hours before the subject is discharged (Table 4).

[r] The times of the prior feeding and first feeding after dosing should be recorded. IMP should be administered every 12 hours or as dosing regimen recommended by the Data Safety Monitoring Committee with a time window of ± 30 minutes.

[s] All the screening assessments (except the RSV Rapid Diagnostic Test) should be completed within 24 hours before Dose 1. A positive RSV Rapid Diagnostic Test result is required on a sample collected within 48 hours before Dose 1.

[t] It is not necessary to repeat the assessment for the -2h to 0 h Pre-Dose 1 timepoint, if the assessment was carried out for screening purposes within the 2 h Pre-Dose 1. However, if the screening assessments were carried out >2 h prior to Dose 1 for screening purposes (i.e. within the first 22 hours of the screening window), the assessment must be repeated between -2h to 0 h Pre-Dose 1.

[u] Allowed time window on the end of treatment safety bloods and urinalysis is +/- 2 days. Should a subject be discharged after Dose 10, the safety blood sample should be obtained prior to discharge.particularly if the parents/legal guardians are unlikely to return for the next visit.

***** **Procedure to be done if subject is in the hospital.**

Table 3b. Schedule of Assessments for Part C subjects discharged prior to Dosing Visit 3

Assessment	Screening	Treatment Phase								Post-Treatment Phase		
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3	Dosing Visit 4	Dosing Visit 5	Follow Up		
		Dose 1			Dose 2	Dose 3	Dose 4	Doses 5 and 6	Doses 7 and 8	Doses 9 and 10	Visit Day 7	Visit Day 14±1 Day	Visit Day 34±1 Day
Time Relative to Dose	-24 h to first dose	-2 h to 0 h	0 h	4-5 h Post-Dose							+40-48 h Post-Dose 10	Day 14	Day 34
Written Informed Consent[a]	X												
Inclusion / Exclusion Criteria	X	X[c]											
RSV Rapid Diagnostic Test	X[b]												
Demographics[d]	X												
Medical History	X												
Prior Medication Review	X												
Physical Examination[e]	X	X[c]									X		
Hydration Status[f]	X	X[c]				X[g]		X[g]	X[g]	X[g]	X		
Body Weight / Length / Head Circumference	X										X	X	X
Vital Signs[h]	X	X[c]		X	X	X	X	X[i]	X[i]	X[i]	X	X	X
12-Lead ECG[j]	X			X		X		(X[k])	(X[k])		X		
ReSVinet Score for Clinicians[l]	X	X[c]				X		X[m]	X[m]	X[m]	X	X	X
Record RSV Signs and Symptoms[n]	X	X[c]			X	X	X	X[o]	X[o]	X[o]	X	X	X
Record Supplemental O_2		X			X	X	X	X	X	X			

Assessment	Screening	Treatment Phase									Post-Treatment Phase		
	Screening Visit	Dosing Visit 1				Dosing Visit 2		Dosing Visit 3	Dosing Visit 4	Dosing Visit 5	Follow Up		
		Dose 1			Dose 2	Dose 3	Dose 4	Doses 5 and 6	Doses 7 and 8	Doses 9 and 10	Visit Day 7	Visit Day 14±1 Day	Visit Day 34±1 Day
Time Relative to Dose	-24 h to first dose	-2 h to 0 h	0 h	4-5 h Post-Dose							+40-48 h Post-Dose 10	Day 14	Day 34
Pulse Oximetry on Room Air		X			X	X	X	X	X	X			
Adapted ReSVinet Scale for Parental Use[p]	X					X		X	X	X	X	X	X
Safety Laboratory Tests (Clinical Chemistry, and Haematology)[q]	X										X[r]		
Urinalysis	X										X[v]		
Randomisation for Eligible Subjects		X											
Pharmacokinetics Blood Sample[s]				X[t,]	X			(X[t,u])	(X[t,u,v])	(X[u])	X		
Nasopharyngeal Swab		X			X[w]	X[w]	X[w]	X	X	X	X	X	X
Concomitant Medication Review	X	X[c]	X	X	X	X[x]	X[x]	X[x]	X[x]	X[x]	X	X	X
Adverse Events Review	X	X[c]	X	X	X	X[x]	X[x]	X[x]	X[x]	X[x]	X	X	X
Study Medication Administration[y]			X		X	X	X	X	X	X			

Footnotes appear on next page.

Abbreviations: ECG = electrocardiogram; h = hours; PK = pharmacokinetic; RSV = respiratory syncytial virus.

Notes: This schedule of assessments is for subjects who met the criteria for early discharge prior to Dosing Visit 3. These subjects are being seen as outpatients and all the assessments should still be completed. All procedures and assessments are presented against the Dosing Visit at which they should be conducted. The actual day(s) on which the visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1. The Follow-up +40–- 48 h Post-Dose 10 on Visit Day 7 could therefore occur on Study Day 7 or 8, depending on when the subject received his or her first dose of IMP.

Observations (SpO2, viral signs, inspection of RSV symptoms) should precede any procedures that manipulate the subject (physical examination, nasopharyngeal swabs, PK sampling). For the physical examination, listen to the lungs first. In any event, the order should be consistent for all the assessment days.

[a] Written informed consent includes the consent for participating in Part C of the study and the written informed consent for the optional Sponsor-provided commercial RSV test.

[b] All the screening assessments (except the RSV Rapid Diagnostic Test) should be completed within 24 hours before Dose 1. A positive RSV Rapid Diagnostic Test result is required on a sample collected within 48 hours before Dose 1.

[c] It is not necessary to repeat the assessment for the -2h to 0 h Pre-Dose 1 timepoint, if the assessment was carried out for screening purposes within the 2 h Pre-Dose 1. However, if the screening assessments were carried out >2 h prior to Dose 1 for screening purposes (i.e. within the first 22 hours of the screening window), the assessment must be repeated between -2h to 0 h Pre-Dose 1.

[d] Demographic data to be collected: date of birth, gender, race, and ethnicity.

[e] Physical examination may also include a symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions (Section 10.1.3.8). For days when IMP is administered, physical examination should be conducted before a dose of IMP is administered.

[f] Refer to Appendix 17.5 for the Dehydration Status Evaluation.

[g] Hydration status post-discharge is to be taken daily at a similar time each day.

[h] Vital signs include body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and should be conducted before PK and nasopharyngeal swab samples, for the respective time points, are taken. For the days without PK and nasopharyngeal swab samples, vital signs should be taken before a dose of IMP is administered.

[i] Vital signs post-discharge are to be taken daily at a similar time each day and must be taken prior to PK and nasopharyngeal swab sampling

[j] 12-Lead ECG to be performed using the centrally provided ECG machine and before PK and nasopharyngeal swab samples are taken. For days when IMP is administered ECG should be performed before a dose of IMP is administered unless a post-dose ECG is scheduled.

[k] Only one ECG is required at either Dosing Visit 3 or Dosing Visit 4. This ECG should be taken either 4-5 h Post-Dose 6 or 4-5 h Post-Dose 7 to coincide with the PK sampling. ECG should be performed prior to the PK sample being collected.

[l] Refer to Appendix 17.6 for the ReSVinet score for clinicians.

[m] ReSVinet score post-discharge are to be taken daily at a similar time each day.

[n] Refer to Appendix 17.4 for RSV Signs and Symptoms

[o] RSV Signs and Symptoms post-discharge are to be taken daily at a similar time each day.

[p] Refer to Appendix 17.2 for the Adapted version of ReSVinet scale for parental use. Upon discharge parents/caregivers are to complete at a similar time each day at home.

[q] At Screening, the AST/ALT values should be obtained from the local laboratory. A Screening blood sample will also need to be sent to the Central laboratory.

[r] Allowed time window on the end of treatment safety bloods and urinalysis is +/- 2 days.

[s] PK samples to be collected Pre-Dose 6 and 4-5 h Post-Dose 6 and 40-48 h Post Dose 10 (Visit Day 7) in all subjects (3 samples). If the Pre- and post-Dose 6 sampling times are at a time that is unsuitable for the subject to return to the clinic or accept a home visit, then these can be taken Pre-Dose 7 and 4-5 h Post-Dose 7 instead.
An additional 3 samples will be collected in the first 9 subjects in each age stratum, if the dose being evaluated in Part C was not evaluated in Part B (i.e. a total of 6 samples will be collected in these 9 subjects). These samples will be taken 4-5 h and 12 h Post-Dose 1 and Pre-Dose 7 (or pre-Dose 8 if the Dose 6 sampling was conducted relative to Dose 7). The DSMC will review the PK data profiles and recommend whether these PK samples are to be taken for subjects enrolled subsequently. Please refer to Table 5 for PK sample schedule.
The actual day for taking each PK sample is dependent on the time when IMP is administered on Visit 1 (Day 1) (morning versus afternoon versus evening); eg, if the subject received their first dose of IMP at 22:00 on Day 1, the post-dose samples due to be taken at 4-5 h, and 12 h would be taken on Day 2 from 02:00 to 03:00, and 10:00 respectively

[t] The timing of the Post-Dose PK samples and assessments in Part C will be 4-5 h Post-Dose.

[u] If the subject is discharged from the hospital and the timing of the Dosing Visit 3 assessments Pre-Dose 6 and Post-Dose 6 fall at a time when it is not appropriate for the subject to return to the hospital or accept a home visit, the Pre-Dose 6 and Post-Dose 6 assessments can be moved relative to Dose 7.

[v] If the PK sampling at Dose 6 is moved relative to Dose 7, then the Pre-Dose 7 PK sample will be moved to Pre-Dose 8. (Note: If the PK sampling is taken relative to Dose 6 then the PK sample should be taken Pre-Dose 7.)

[w] If the subject is discharged from hospital, a nasopharyngeal swab sample should be obtained prior to discharge. Note: this sample is not required if the previous sample was taken less than 12 hours before the subject is discharged. See Table 4 for nasopharyngeal swab sample schedule. Samples taken post-discharge at Dosing Visits 3, 4 and 5 are to be spaced evenly such that the nasopharyngeal swab samples are taken daily at a similar time each day. For instance, the samples should either be taken Pre-Dose 5, Pre-Dose 7 and Pre-Dose 9, OR Pre-Dose 6, Pre-Dose 8 and Pre-Dose 10.

[x] After discharge the assessment for concomitant medication and Adverse events should be conducted daily during the outpatient visit, whilst the parent/caregiver will record in the Patient Booklet their assessment for doses given at home.

[y] IMP should be administered every 12 hours or as dosing regimen recommended by the Data Safety Monitoring Committee with a time window of ± 30 minutes. The times of the prior feeding and first feeding after dosing should be recorded.

( ) Denote samples and assessments that can be taken on either Dosing Visit

Table 4. Nasopharyngeal Sampling Schedule for the Study

Part	Dosing Visit 1					Dosing Visit 2	Dosing Visit 3	Dosing Visit 4	Dosing Visit 5	Visit Day 7	Visit Day 14	Visit Day 34
A	-2 h to 0 h Pre-Dose (1 sample)	*12 h Post- Dose 1* [bc] *(optional)*	1 sample collected 24 h Post-Dose [b]	*1 sample collected at 36 h Post-Dose*[bc] *(optional)*	1 sample at 48 h Post-Dose 1[b]	NA	NA	NA	NA	NA	NA	NA
B	-2 h to 0 h Pre-Dose (1 sample)	*12 h Post- Dose 1 (Pre-Dose 2)*[bc] *(optional)*	NA	NA		1 sample collected Pre-Dose 3[b]. *Pre-Dose 4*[c] *sample (optional)* Up to 2 samples in total[b]	1 sample collected prior to each dose; Up to 2 samples in total[ab]	1 sample collected Pre-Dose 7[b]. *Pre-Dose 8*[c] *sample (optional)* Up to 2 samples in total*[b]	1 sample collected Pre-Dose 9[b] *Pre-Dose 10*[c] *sample (optional).* Up to 2 samples in total*[b]	+40-48 h Post-Dose 10	NA	NA
C	-2 h to 0 h pre-dose (1 sample)	*12 h Post Dose 1 (pre-dose 2)*[bc] *(optional)*	NA	NA		1 sample collected prior to each dose. *Pre-Dose 4*[c] *sample (optional).* Up to 2 samples in total[b]	1 sample collected prior to each dose; Up to 2 samples in total[ab]	1 sample collected Pre-Dose 7[b]. *Pre-Dose 8*[c] *sample (optional).* Up to 2 samples in total*[b]	1 sample collected Pre-Dose 9[b]. *Pre-Dose 10*[c] *sample (optional).* Up to 2 samples in total*[b]	+40-48h Post Dose 10	1 Sample	1 Sample
Part C subjects discharged prior to Dosing Visit 3:												
C	-2 h to 0 h pre-dose (1 sample)	*12 h Post Dose 1 (pre-dose 2)*[b,c] *(optional)*	NA	NA		1 sample[a,b] collected prior to either Dose 3 or 4.	1 sample[b,d,e] collected prior to either Dose 5 or 6	1 sample[b,e] collected prior to either Dose 7 or 8	1 sample[b,e] collected prior to either Dose 9 or 10	+40-48h Post Dose 10 (1 sample)	1 Sample	1 Sample

Footnotes appear on next page.

Abbreviations: h = hours; IMP = investigational medicinal product; NA = not applicable

Notes:

All procedures and assessments are presented against the Dosing Visit at which they should be conducted. The actual day(s) on which the visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1. The Follow-up +40-48 h Post-Dose 10 on Visit Day 7 could therefore occur on Study Day 7 or 8, depending on when the subject received his or her first dose of IMP.

CCI [redacted]

[a] If the subject is discharged from hospital, a nasopharyngeal swab sample should be obtained prior to discharge. Note: This sample is not required if the previous sample was taken less than 12 hours before the subject is discharged.

[b] Nasopharyngeal swab sampling window is 60 minutes.

[c] Pre-dose 2, 4, 8 and 10 are optional nasopharyngeal swab samples in study Part B.

[d] If the subject is discharged prior to completion of Dosing Visit 3 it may be necessary to move the Pre-Dose 6 nasopharyngeal swab sample relative to Dose 7

[e] Samples taken post-discharge at Dosing Visits 2, 3, 4 and 5 are to be spaced evenly such that the nasopharyngeal swab samples are taken daily at a similar time each day. For instance, the samples should either be taken Pre-Dose 3, Pre-Dose 5, Pre-Dose 7 and Pre-Dose 9, OR Pre-Dose 4, Pre-Dose 6, Pre-Dose 8 and Pre-Dose 10.

* Procedure to be done if subject is in the hospital.

Table 5. PK Sampling Schedule for the Study

Part	Treatment Phase					Post Treatment Phase	Total Number of Samples
	Dosing Visit 1	Dosing Visit 2	Dosing Visit 3	Dosing Visit 4	Dosing Visit 5	Visit Day 7	NA
A: Single Dose	1-2 h, 4-5 h, 6-8 h, 12 h[a], 18-24 h	NA	NA	NA	NA	NA	5
B*: Multiple Dose	1-2 h or 4-5 h or 6-8 h Post-Dose 1, 12 h[a] Post-Dose 1 (Pre-Dose 2)	NA	Pre-Dose 6, 1-2 h or 4-5 h or 6-8 h Post-Dose 6.	12 h[a] Post-Dose 6 (Pre-Dose 7)	NA	40-48 h Post-Dose 10	6
C**: Multiple Dose	4-5 h Post-Dose 1[c], 12 h[a] Post-Dose 1 (Pre-Dose 2)	NA	Pre-Dose 6[bc] 4-5 h Post-Dose 6 [bc]	12 h[a] Post-Dose 6 (Pre-Dose 7)	NA	40-48 h Post-Dose 10 [b]	3 or 6[b]
Part C subjects discharged prior to Dosing Visit 3:							
*C**: Multiple Dose*	4-5 h Post-Dose 1[c], 12 h[a] Post-Dose 1 (Pre-Dose 2)	NA	(Pre-Dose 6[b,c,d]) (4-5 h Post-Dose 6 [b,c,d]) (12 h[a,d] Post-Dose 6/Pre-Dose 7) *OR* (Pre-Dose 7[b,c,d]) (4-5 h Post-Dose 7 [b,c,d]) (12 h[a,d] Post-Dose 7/Pre-Dose 8)		NA	40-48 h Post-Dose 10 [b]	3 or 6[b]

Footnotes appear on next page.

Abbreviations: h = hours; IMP = investigational medicinal product; NA = not applicable; PK = pharmacokinetic.

Notes: All procedures and assessments are presented against the Dosing Visit at which they should be conducted. The actual day(s) on which the visit falls is dependent upon the time that investigational medicinal product (IMP) is administered during Dosing Visit 1. The Follow-up +40-48 h Post-Dose 10 on Visit Day 7 could therefore occur on Study Day 7 or 8, depending on when the subject received his or her first dose of IMP.

* For PK Part B: After the review of PK analysis from Part A, it will be decided if the PK sample after the First Dose will be taken 1-2 h, 4-5 h Post Dose 1 or 6-8 h Post-Dose 1. The same time point will be taken on Dosing Visit 3 (either 1-2 h, 4-5 h or 6-8 h Post-Dose 6). Based on the Part A PK analysis, it will be decided if the Samples planned relative to Dose 6 should stay as planned or shifted relative to Dose 10 with the same time structure. In case the PK samples are shifted relative to Dose 10, then an additional PK sample 18-24 h Post-Dose 10 will be taken.

** For PK Part C: The same PK time point Post-Dose 6 will be taken as in Part B, at 4-5 h Post-Dose 6.

[a] The 12-hour PK sampling window is 30 minutes.

[b] If the PK profile for a dose to be evaluated in Part C *was evaluated* in Part B, only 3 PK samples will be drawn: Pre-Dose 6, 4-5 h Post Dose 6 sample and Visit Day 7. If the PK profile *was not evaluated* in Part B, a total of six PK samples will be drawn as detailed in the table above.

[c] The timing of the Post-Dose PK samples and assessments in Part C will be 4-5 h Post-Dose.

[d] If the subject is discharged after completion of Dosing Visit 1 it may be necessary to move the Pre-Dose 6 and 4-5 h Post-Dose 6 PK sampling relative to Dose 7. If the PK Tmax sampling is moved relative to Dose 7 then the Pre-Dose 7 PK sample will be moved to Pre-Dose 8

( ) Denote samples and assessments that can be taken on either Dosing Visit

8.2 Overall Study Design and Plan: Description

The clinical study consists of 3 parts:

- Part A is an open-label, multicentre, single dose study in infants hospitalised with RSV LRTI
- Part B is a randomised, double-blind, placebo-controlled, multicentre multiple dose study in infants hospitalised with RSV LRTI
- Part C is a randomised 1:1:1, double-blind, placebo-controlled, multicentre, multiple-dose study comparing two dose levels of RV521 to matching placebo in infants ≥1 months and ≤36 months hospitalised with RSV LRTI

The number of subjects enrolled in Parts A and B of the study will depend on the safety and PK data from the group of subjects enrolled in specified cohorts and the subsequent recommendation of the Data Safety Monitoring Committee (DSMC). The DSMC will review all available safety and PK data collected from the first 3 subjects and subsequent 3 subjects in Cohort 1 and determine the starting dose for subjects in Cohort 2 (either 2 mg/kg or an adjusted dose based on Cohort 1 safety and PK data). The DSMC may recommend a dose adjustment (either a reduction or an escalation) and/or regimen adjustment (Part B only) for subsequent subjects because of the observation of an unexpected safety/tolerability profile and/or differences between the observed and predicted exposure resulting from a specified dose of RV521.

Part A

Part A of the study will be conducted across 2 cohorts and will comprise 2 age groups:

- Cohort 1: subjects ≥ 6 months to ≤ 36 months
- Cohort 2: subjects ≥ 1 month to < 6 months

The proposed starting doses of RV521 of 2.5 mg/kg for subjects ≥ 6 months to ≤ 36 months of age (Cohort 1) and 2 mg/kg for subjects ≥ 1 month to < 6 months of age (Cohort 2) are expected to deliver a specified group mean exposure (1× EC_{90} at trough concentration) based on PK modelling and simulation using existing clinical data in healthy adult subjects (CCI and CCI) and nonclinical data. Pharmacokinetic data from groups of 3 subjects in Cohort 1 and Cohort 2 will be reviewed to identify any differences between the observed and predicted exposure resulting from a specified dose of RV521. Safety data will be sent to the DSMC for review prior to any dose adjustment.

Enrolment into Part A of the study will commence with the older subjects (Cohort 1).

Any adjustment(s) of dose level that are required within a cohort will occur in a sequential manner. A maximum of 2 dose adjustments per cohort are planned. Thus, a minimum of 12 subjects (6 per cohort) and a maximum of 24 subjects (12 per cohort) may be enrolled in Part A.

Part B

Part B will be conducted across 3 cohorts (Cohorts 3, 4, and 5) comprising the following age groups:

Cohort 3: ≥ 6 months to ≤ 36 months

Cohort 4: ≥ 1 month to < 6 months

Cohort 5 ≥ 1 month to ≤ 36 months

After review of the safety and PK data from a specific age group enrolled in Part A, the DSMC will determine the dosage and dosing regimen to be used in that age group in Part B, such that the target group mean trough concentration is approximately equivalent to 3× EC_{90}, and approve the start of enrolment in that specified age group, ie, Cohort 3 can start after Cohort 1 (Part A) has been finalised and Cohort 4 can start after Cohort 2 (Part A) has been finalised. It is anticipated that subjects enrolled in Part B of the study will receive RV521 or placebo BID, 12 hours apart, for a period of 5 consecutive days (total of 10 doses). However, the dosing regimen may be adjusted depending on the DSMC recommendations.

Groups of 4 subjects will be randomised to receive RV521 or placebo (3:1) in Cohort 3 and Cohort 4, with enrolment occurring in parallel. It is envisioned that data from a group of 4 subjects will be sufficient to confirm the dose exposure relationship for RV521 administered according to a multiple dosing regimen and therefore the DSMC will review all available safety and PK data collected from the first group of 4 subjects in each cohort.

In order to identify the optimum dosage and dosing regimen in each age group, a maximum of 2 dosage/dosing regimen adjustments is assumed in either or both of the Cohorts 3 and 4. Subjects ≥ 6 months to ≤ 36 months of age can be enrolled in Cohort 5 after the completion of Cohort 3 and subjects ≥ 1 month and < 6 months can be enrolled in Cohort 5 after the completion of Cohort 4. Cohort 5 will be opened when either Cohort 3 or Cohort 4 is complete. Enrolment in Cohort 5 will continue until 24 evaluable subjects have received RV521 or placebo (2:1). The 4 subjects in the dose group that received the specified dose from each of Cohorts 3 and/or 4 will contribute to this overall total. Thus a minimum of 24 subjects and a maximum of 40 subjects (assuming 2 adjustments per age group) may be enrolled in Part B.

Part C

Based on the analysis of the safety, PK, and antiviral data following the completion of Part B, Part C will commence to confirm the antiviral effects of the two dose levels of RV521 vs. placebo. The dose levels will be selected based on the paediatric PK model, and will target equivalent RV521 exposure levels between the two age groups (≥ 1 month to < 6 months and ≥ 6 months to ≤ 36 months). The DSMC will evaluate safety data at intervals specified in the DSMC Charter.

Part C will evaluate 111 subjects total (37 per treatment arm) aged ≥ 1 month to ≤ 36 months with an aim to have at least 34 evaluable subjects per treatment group. The primary endpoint will be the time-weighted average change from Baseline to Day 7 in RSV viral load measured in nasopharyngeal swabs by RT-qPCR comparing two dose levels of RV521 vs. placebo.

Secondary endpoints will assess the safety, and efficacy of two dose levels of RV521 vs. placebo. Dose levels in Part C will be selected following the analysis of PK data, tolerability and safety from Part B. Two doses (RV521 age group specific high dose and RV521 age group specific low dose) will be selected for inclusion in Part C. The high dose will be selected for each age group to target approximately 90% of subjects achieving the target trough concentration for efficacy (3x EC90), while not exceeding the upper safety limit, based on the paediatric PK model. The low dose will be selected such that the target trough level of 3xEC90 is achieved in approximately 75% of the subjects. The high dose may be the highest tolerated dose from Part B, or a higher twice daily dose of RV521, depending on the safety, tolerability and PK data from Part B.

Subjects in Part C will be stratified by age (≥1 to < 6 months of age vs. ≥ 6 months to ≤ 36 months of age) and randomised in a 1:1:1 ratio. Both age strata will be enrolled in parallel. To maintain the double-blind, subjects randomised to placebo will be allocated to low volume (to match the volume associated with the lowest tested dose of RV521) or the higher volume (to match the highest tested dose of RV521).

The DSMC will periodically review the safety, tolerability, and PK in Part C in accordance with the DSMC Charter, and may make recommendations about study continuance or dose termination. In the event that a higher dose is selected for evaluation in Part C than was evaluated in Part B, the safety and PK results of the first 9 subjects in each age stratum (3 subjects per arm) will be reviewed in an unblinded manner by the DSMC. The primary focus of this DSMC review will be on the safety and PK profile of the subjects receiving the new higher dose. In the absence of any safety signals in the first 9 subjects in each age stratum, the Safety Physician may determine that continued randomisation of additional subjects is warranted during the DSMC review period. In the event that there is a safety signal of concern, the Safety Physician will make the determination that all randomisation will be halted until the DSMC has completed their review and has recommended that further randomisation may continue. An earlier meeting of the DSMC can be convened, as warranted, and based on the results of the DSMC review, the DSMC may recommend to the Sponsor that a dose of RV521 be terminated. The Sponsor will make the final decision.

Duration of Hospitalisation

Part A: All study visits should be conducted in the hospital setting, with the exception of the Telephone Follow-Up. Day 7 visit following the single dose (subject follow up), if the subject has been discharged home, will be by telephone.

Part B: Subjects should remain in the hospital for at least 3 dosing days, and through the sample collection of Dosing Visit 3 to the 12 hours Post-Dose 6 PK sample (pre-Dose 7). Evaluations listed at Dosing Visit 4 and Dosing Visit 5 (see Table 2) should be done in the event that the subject remains in hospital. The last evaluation will be conducted 40 to 48 hours after the last dose of IMP is administered. This may be conducted in hospital, or in the event the subject has been discharged, in an outpatient setting.

Part C: Subjects should ideally remain in the hospital for at least 48 hours post randomisation to accommodate taking the first 4 doses of IMP and collection of the assessments scheduled for Dosing Visit 1 and Dosing Visit 2. If the subject remains in hospital, the assessments for Dosing

Visit 3, Dosing Visit 4 and Dosing Visit 5 should be conducted as specified (see Table 3a). In the event that a subject is to be discharged after Dosing Visit 3 and the 12 hours Post-Dose 6 PK sample (pre-Dose 7) is required, this sample should be taken prior to discharge.

If the subject has met the criteria for early discharge prior to Dosing Visit 3 and is being seen as an outpatient the required assessments should still be completed and are listed in Section 9.4 and Table 3b. In this circumstance upon discharge, the subject should return to the clinic or outpatient facility for the required assessments for the remaining Dosing Visits (e.g Dosing Visits 2, 3, 4 and 5) (see Table 3b). If this is not possible, an appropriately trained healthcare professional (such as home health nurse or equivalent) will conduct home visits. The timing of the clinic or home visits should be arranged to ensure that the post-dose ECG is performed and the pre- and post-dose PK samples are collected before and after either Dose 6 or Dose 7, depending on the time of day of these doses. This is to ensure that these parameters are evaluated at steady state. It is envisaged that the follow up evaluations, and Visit Day 7 (40-48 h Post-Dose 10), Visit Day 14, and Visit Day 35, will be conducted in outpatient clinics, but home visits can be conducted if this is not possible.

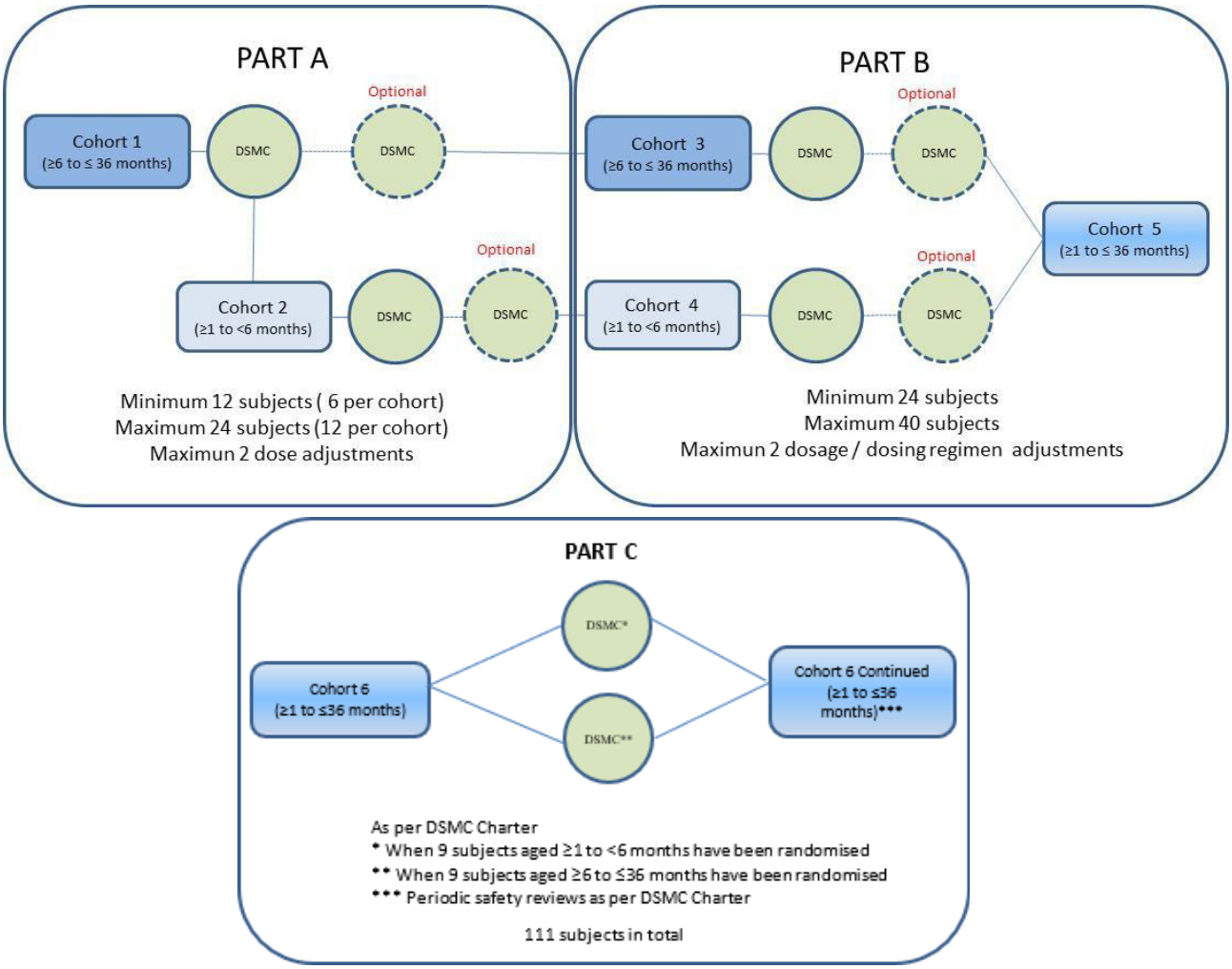
When a subject is discharged from hospital and IMP will be administered at home (Parts B and C), the parent/legal guardian (and/or another caregiver, if required) will be trained in the storage, preparation, and administration of IMP at home and will be issued with a Patient Booklet to record the relevant details of IMP administration. The parent/legal guardian will be instructed how to complete the Patient Booklet accurately and these instructions may be reinforced with phone calls during outpatient dosing to parents and/or caregivers.

8.3 Discussion of Study Design

8.3.1 Study Design

This is a multicentre, 3-part study to evaluate safety, tolerability, PK, PD, and antiviral effect of single and multiple dosing of RV521 in infants hospitalised due to RSV LRTI. Due to the adaptive study design, the number of enrolled subjects may vary depending on the obtained PK and safety profiles.

Figure 1. Study Design



Abbreviation: DSMC = Data Safety Monitoring Committee.

The selection of the starting doses was estimated using a population PK approach according to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) requirements (FDA CDER/CBER Guidance for Industry page; EMEA/CHMP Guideline page). Pharmacokinetic data from healthy adult subjects administered RV521 in clinical studies CCI and CCI (Section 6.4) was used to build a population PK model using Phoenix NLME software. The model was verified using standard checks, such as Visual Predictive Check plots, bootstrap analysis, and goodness of fit plots (EMA, 2007), which compare the predicted concentration values to actual observed concentrations as well as show the residual differences between predicted and actual concentrations as an assessment of model validity. The terms for allometric scaling and maturation factor in an infant population, depending on post-natal age and body weight were added to the model to simulate PK profiles and resulting exposure in infants. The model was informed with the available demographics covariates to allow the incorporation of a non-linear dose effect, formulation and/or food effect, and available body weight and age data to support extrapolation to infants.

The simulated exposure was restricted by the lower bound for efficacy, using the EC_{90} for RSV inhibition, applied to the unbound concentration after the first dose (Dose 1) at the end of the dosing interval of 12 hours (C_{min}). This equated to a total RV521 concentration of [redacted] (converted from unbound) (Figure 2).

To assess where the upper limit of the exposure may be set, the C_{max} and AUC_{tau} for the last dose (Dose 10) of the BID dosing regimen in adult subjects dosed at 350 mg of RV521 (Clinical Study [redacted] were used as a guideline and are presented in a separate report (Syneos Health, 2018). Therefore the upper limit for dose levels will be selected such that the peak plasma exposure levels do not exceed the group mean values observed in Clinical Study [redacted] (C_{max} of 294 ng/mL) and total exposure, as measured by AUC_{tau} in the same study, will not exceed 2500 ng × h/mL.

The resulting proposed starting doses are 2 mg/kg for infants ≥ 1 to < 6 months of age and 2.5 mg/kg for infants ≥ 6 to ≤ 36 months of age (Table 6 and Table 7, respectively).

Table 6. Expected Exposure for Infants ≥ 1 to < 6 Months of Age after Administration of 2 mg/kg RV521

Parameter	Age, years	Boys			Girls		
		Median	10th Percentile	90th Percentile	Median	10th Percentile	90th Percentile
C_{min} Dose 1 ng/mL	[redacted]						
C_{max} Dose 10 ng/mL	[redacted]						
AUC_{tau} Dose 10 h × ng/mL	[redacted]						
C_{min} Dose 10 ng/mL	[redacted]						

Abbreviations: AUC_{tau} = area under the plasma concentration-time curve from zero to the end of last dosing interval; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration.

Table 7. Expected Exposure for Infants ≥ 6 to ≤ 36 Months of Age after Administration of 2.5 mg/kg RV521

Parameter	Age, years	Boys Median	Boys 10th Percentile	Boys 90th Percentile	Girls Median	Girls 10th Percentile	Girls 90th Percentile
C_{min} Dose 1 ng/mL	CCI						
	CCI						
C_{max} Dose 10 ng/mL	CCI						
	CCI						
AUC_{tau} Dose 10 h × ng/mL	CCI						
	CCI						
C_{min} Dose 10 ng/mL	CCI						
	CCI						

Abbreviations: AUC_{tau} = area under the plasma concentration-time curve from zero to the end of last dosing interval; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration.

Figure 2. Trough Concentrations for Dose 1 and Dose 10 of BID Dosing vs Body Weight Adjusted Dose in Infants of Different Age Groups

For the first administration of RV521 in infant subjects, an initial single-dose design is considered appropriate to assess the safety profile of the drug in a way that minimises subject risk. Furthermore, the planned doses are expected to produce quantifiable RV521 concentrations that will support the refinement of the population PK model. Three subjects in the older age group will initially receive a single dose of RV521. Following review of the PK data, a second group of 3 subjects in the older age group will receive a single dose of RV521 either at the same dose level or at an adjusted dose based on the PK data. The DSMC will review all available safety and PK data collected from the first 3 subjects and subsequent 3 subjects in Cohort 1 and determine the starting dose for subjects in Cohort 2 (either 2 mg/kg or an adjusted dose based on Cohort 1 safety and PK data). Pharmacokinetic data from 3 subjects in Cohort 1 and Cohort 2 will be reviewed to identify any differences between the observed and predicted exposure resulting from a specified dose of RV521. The data will be used for verification and refinement of the population PK model currently based on the extrapolation of adult data to the paediatric population. The resulting refined population PK model, in addition to the safety data, will guide further dosing decisions.

The actual number of subjects enrolled in Parts A and B of the study is dependent upon the recommendation of the DSMC, who will review safety and PK data from subjects enrolled in the

specified cohorts (Section 8.2). The DSMC may recommend a dose adjustment (either a reduction or an escalation, Part A and Part B) and/or a regimen adjustment (Part B only) for subsequent subjects due to the observation of an unexpected safety/tolerability profile and/or differences between the observed and predicted exposure resulting from a specified dose of RV521.

This study provides an opportunity to explore CCI in a number of subjects considered sufficient to adequately determine dose levels that are safe and pharmacologically active, thereby informing the selection of doses and dosing regimens to be evaluated in future studies.

In Part B and Part C of the study, the double-blind placebo-controlled design ensures that Investigators and the subject's parent(s)/legal guardian(s) will be blinded to whether the subject receives RV521 (active drug) or placebo, so as to minimise any bias when the safety and tolerability assessments are performed. Furthermore, limited numbers of placebo subjects are included in the study to allow for a more robust interpretation of the data.

8.3.2 Quality Management and Risk Evaluation

This protocol has been evaluated to identify those processes and data that are critical to assure human subject protection and the reliability of study results.

Predefined quality tolerance limits have been established and documented in the functional plans, which take into consideration the medical and statistical characteristics of the variables as well as the statistical design of the study, thereby identifying systematic issues that could impact subject safety or data integrity. Detection of deviations from the predefined quality tolerance limits will trigger an evaluation to determine if action is needed. Any important deviations from the predefined quality tolerance limits and remedial actions taken will be described in the clinical study report.

Risk control measures will be periodically reviewed to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

8.4 Selection of Study Population

8.4.1 Number of Planned Subjects

Approximately 175 subjects (24 subjects in Part A, 40 subjects in Part B, and approximately 111 subjects in Part C) will be evaluated. Eligible subjects ranging in age from ≥ 1 month to ≤ 36 months who are hospitalised because of RSV LRTI will be enrolled in the study. It is anticipated that 102 to 126 subjects will receive RV521 (12 to 24 subjects in Part A, 16 to 28 in Part B, and approximately 74 in Part C), and 45 to 49 subjects will receive placebo (8 to 12 subjects in Part B and approximately 37 in Part C). The total number of subjects to finally be enrolled will depend on the number of DSMC-recommended dosage/dosing regimen adjustments in Parts A and B and whether the DSMC recommend dropping any doses from Part C following their review.

The final number of subjects enrolled in Part C will be dependent upon the number of evaluable subjects and may include any eligible subjects who are in the final stages of screening when the target of 110 enrolled subjects is attained.

8.4.2 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria at the Screening Visit:

1. Male or female ≥ 1 month and ≤ 36 months of age.
2. Weigh ≥ 3.5 kg (Parts A, B, and C) but ≤ 18 kg (Part C only).
3. Clinical diagnosis of LRTI defined by
    a. Evidence of respiratory infection by one or both of the following with or without fever
        i. Rhinitis/coryza
        ii. Cough

        AND

    b. Evidence of LRTI by the presence of one or more of the following:
        i. Increased respiratory rate PLUS other evidence of lower respiratory tract disease (eg, laboratory or radiographic evidence)
        ii. Increased respiratory effort as evidenced by one or more of the following:
            1. Grunting with expiration
            2. Nasal flaring
            3. Retraction: intercostal or subcostal
        iii. Wheezing: audible or on chest auscultation
4. A positive RSV diagnostic test (RSV infection confirmed either according to routine site practice [polymerase chain reaction or diagnostic quick test], or using a [Sponsor-provided] commercial kit).
5. Hospitalised because of RSV LRTI (bronchiolitis or bronchopneumonia).
6. For Part B, symptoms of LRTI must be present for no more than 1 week before the Screening Visit, with the first day of symptoms counting as Day 1.
7. For Part C, symptoms of LRTI must be present for no more than 5 days prior to Screening Visit, with the first day of symptoms counting as Day 1.
8. Expected to remain in the hospital for minimum of 3 days (administration of 6 doses) for Part B only.
9. The parent(s)/legal guardian(s) of the subject have provided written informed consent for the subject to participate.

10. The parent(s)/legal guardian(s) are able and willing to comply with the study protocol.

8.4.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable at the Screening Visit:

1. Premature (gestational age less than 37 weeks) AND < 1 year of post-natal age.
2. Known to have significant comorbidities, including genetic disorders (eg, trisomy 21); cardiopulmonary diseases (eg, haemodynamically significant congenital heart disease); significant pulmonary disease (eg, bronchopulmonary dysplasia, cystic fibrosis); history of surgery for diaphragmatic hernia; any hereditary or acquired metabolic diseases, haematological or other malignancy; or is known to be HIV positive; or has evidence of severe neurologic impairment or developmental delay that would limit the ability to administer study drug or evaluate the safety or clinical response to IMP.
3. Current respiratory insufficiency likely to require imminent invasive mechanical ventilation (Part C only).
4. Malformation of the gastrointestinal tract including unresolved pyloric stenosis, history of necrotising enterocolitis, short bowel, or other significant condition that would alter drug absorption or increase the risk of diarrhoea.
5. Any clinically significant electrocardiogram (ECG) abnormalities.
6. Known to be immunocompromised.
7. High probability of asthma (per GINA Guidance 2020) with all of the following:
    a. Symptoms (cough, wheeze, heavy breathing) for > 10 days during previous upper respiratory infections
    b. History of > 3 episodes per year or severe episodes and/or night worsening
    c. Between episodes, child has cough, wheeze, or heavy breathing during play or when laughing
    d. Allergic sensitisation, atopic dermatitis, food allergy, or family history of asthma
8. Suspected of having a clinically significant bacterial infection, as indicated by symptoms or laboratory findings consistent with a bacterial infection, including but not limited to: elevated white blood cell count, elevated C-reactive protein, chest X-ray consistent with bacterial pneumonia, unstable vital signs, hypotension, or evidence of shock or poor perfusion.
9. Has significant oral and/or maxillofacial malformations that would limit the ability to administer IMP.
10. History of renal failure including renal anomalies likely to be associated with renal insufficiency (eg, clinical conditions of renal dysplasia, polycystic renal disease, renal agenesis).
11. Clinical evidence of hepatic decompensation (eg, hepatic disorder with associated coagulopathy or associated encephalopathy) or significantly elevated liver enzymes

(aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] > 3 × the upper limit of normal).

12. History of epilepsy or seizures. Subjects with a history of febrile seizures will be permitted to enrol.
13. Allergy to test medication or constituents.
14. Known to be concurrently infected with COVID-19 virus (SARS-CoV-2).
15. Requires any prohibited medication/therapy during the course of the study:
    a. Requires inhaled, oral, or IV corticosteroids therapy during the dosing period of the study.
    b. Has taken within 21 days before dosing, or requires during the dosing period of the study, any drug that could impact on the PK of the investigational product including potent inhibitors or potent and moderate inducers of CYP P450s (as listed in Appendix 17.3).
    c. Has taken within 21 days before dosing, or requires during the dosing period of the study, any prescription medications, over-the-counter (OTC) medications, herbal remedies or dietary supplements containing CCI [redacted] or the consumption of CCI [redacted]-containing products CCI [redacted].
    d. Requires the use of Heliox, leukotriene receptor antagonist (eg, montelukast), exogenous surfactant, or mucolytics during the dosing period of the study.
16. Has received 1 or more doses of palivizumab at any time before Screening or received treatment with antiviral therapy for RSV (eg, ribavirin or intravenous [IV] immunoglobulin) within 3 months before the Screening Visit. **Note**: Subjects eligible for palivizumab treatment or other RSV prophylaxis cannot be included in the study.
17. The subject's parent(s) or legal guardian(s) is a study team member (ie, has direct involvement in this study or other studies under the direction of the Investigator or the study centre) or is a family member of either the Investigator or other team members.
18. Currently participating in any investigational study or at the time of screening, has received an investigational product within 3 months or within 5 half-lives of the investigational product, whichever is longer.
19. Any other reason which in the opinion of the Investigator makes the participant unsuitable for a clinical trial.

8.4.4 Removal of Subjects from Therapy or Assessments

Subjects may be withdrawn from the study for any of the following reasons:

- Parent/legal guardian request
- Use of prohibited concomitant medication/therapy

- Non-compliance with the protocol
- Lost to follow-up
- Occurrence of AEs that are not compatible with the continuation of the subject in the study, in the Investigator's opinion, or that make it unacceptable to the subject's parent/legal guardian for them to continue
- Investigator request
- Intercurrent illness
- Sponsor request
- Becoming critically ill with respiratory insufficiency leading to the requirement for mechanical ventilation/positive airway pressure (PAP)/high-flow oxygen
- Randomisation code broken prematurely (Parts B and C)

Parents/legal guardians are free to withdraw their children from the study at any time without providing reason(s) for withdrawal and without prejudice for receiving further treatment. The reason(s) for withdrawal will be documented in the case report form (CRF). Parents/legal guardians who choose to withdraw their child from the study will be encouraged to allow their child to complete the same final evaluations as subjects completing the study according to the protocol, particularly safety evaluations.

All reasonable efforts should be made to contact the parent/legal guardian of a subject who is lost to follow-up. These efforts must be documented in the subject's file.

8.4.5 Interruption of Dosing or Enrolment

Parts A, B and C

- The study will be halted if RV521 systemic exposures observed in an individual subject at a dose level, or projected for a subsequent dose level, which are equal or exceed those values observed in Clinical Trial Study CCI : Cmax of 294 ng/mL and total exposure AUCtau of 2500 ng.h./mL.

If this dosing stopping criterion is fulfilled, further dosing at the assessed dose level or higher dose level will be halted. Restart of dosing will only be possible if agreed by the DSMC (and after local regulatory authority approval, if required).

Parts A and B

Adverse events, singularly or cumulatively, may interrupt further dosing or enrolment until an evaluation can be made and a determination made as to the safety of proceeding. The following events will result in such an interruption, pending an evaluation by the DSMC.

- Any death of a subject during participation in the study
- An SAE deemed related to IMP by the Investigator

- Two or more SAEs of a similar type irrespective of attributability by the Investigator(s)
- Any accumulation of AEs of Grade 3 or higher, including laboratory abnormalities that, in the opinion of the DSMC, Medical Monitor, or ReViral Medical Expert, represent an unacceptable risk to subjects enrolled in the trial.

Part C:

The study will be paused immediately and a DSMC meeting will be convened to review the available safety data if either of the following criteria are met:

- At any point in the study, two or more subjects experience the same or a similar SAE that is rated by the Investigator as possibly, probably, or definitely related to RV521
- At any point in the study, two or more subjects experience the same or a similar AE that is Grade 3 or higher using the CTCAE scale, including laboratory abnormalities that, in the opinion of the DSMC, Medical Monitor, or ReViral Medical Expert, represent an unacceptable risk to subjects enrolled in the trial.

If any of the above stopping/pausing criteria are fulfilled in any study part, restart of dosing will only be possible if agreed by the DSMC (and after local regulatory authority approval, if required).

Should a clear non-IMP cause for any of the above be identified, or if the subjects(s) are not receiving RV521 (ie, in the placebo group), the study may continue.

If the study is terminated, the Investigators will be informed of the reason for study termination.

Unless the study is stopped in accordance with the stopping guidelines, a subject enrolled in Part A who is withdrawn from the study before they have been administered IMP will be replaced. In addition, subjects enrolled in Part A will be replaced if emesis occurs within 30 minutes post-dosing, although these subjects should remain in the study such that all planned study assessments can be conducted. In Part A subjects may also be replaced if they do not ingest all of the administered dose. In Part B, subjects will be replaced if emesis occurs within 30 minutes of administration of Dose 6 (or Dose 3 if dosing is according to a once-daily regimen). These subjects should remain in the study such that all planned study assessments can be conducted. In Part B and Part C, a subject may be replaced if they have not been administered IMP or have not ingested/completed at least 6 doses of IMP (or 3 doses by once-daily regimen).

8.5 Investigational Medicinal Products

8.5.1 Investigational Medicinal Products Administered

Administration of IMP should occur within 12 hours of randomisation for all subjects across all cohorts, in accordance with their assigned dosage and dosing regimen.

The times of completion of feeding prior to dosing and commencement of the first feeding after dosing should be recorded in the subject's source notes.

IMP administration will be by oral route, either via syringe or nasogastric tube.

Part A:

A single oral dose of RV521will be administered in Part A. The proposed starting doses are: 2.5 mg/kg for subjects in Cohort 1 (≥ 6 months to ≤ 36 months of age) and 2 mg/kg for subjects in Cohort 2 (≥ 1 month to < 6 months of age). These dose levels are anticipated to achieve a target exposure equivalent to 1× EC_{90} at trough concentration in each age group. A maximum of 2 dose adjustments will be allowed for each cohort.

Part B:

Part B will be conducted across 3 cohorts (Cohorts 3, 4, and 5) comprising the following age groups:

Cohort 3: ≥ 6 months to ≤ 36 months

Cohort 4: ≥ 1 month to < 6 months

Cohort 5: ≥ 1 month to ≤ 36 months

Following review of the safety and PK data from a specific age group enrolled in Part A, the DSMC will determine the dosage and dosing regimen to be used in that age group in Part B, such that the target group mean trough concentration is approximately equivalent to 3× EC_{90}, and approve the start of enrolment in that specified age group, ie, Cohort 3 can start after Cohort 1 (Part A) has been finalised and Cohort 4 can start after Cohort 2 (Part A) has been finalised. It is anticipated that subjects enrolled in Part B of the study will receive RV521 or placebo BID, 12 hours apart, for a period of 5 consecutive days (total of 10 doses). However, the dosing regimen may be adjusted depending on the DSMC recommendations.

Groups of 4 subjects will be randomised to receive RV521 or placebo (3:1) in Cohort 3 and Cohort 4, with enrolment occurring in parallel. It is envisioned that data from a group of 4 subjects will be sufficient to confirm the dose exposure relationship for RV521 administered according to a multiple dosing regimen and therefore the DSMC will review all available safety and PK data collected from the first group of 4 subjects in each cohort. In order to identify the optimum dosage and dosing regimen in each age group, a maximum of 2 dosage/dosing regimen adjustments is assumed in either or both of the Cohorts 3 and 4. Subjects ≥ 6 months to ≤ 36 months of age can be enrolled in Cohort 5 after the completion of Cohort 3 and subjects ≥ 1 month and < 6 months can be enrolled in Cohort 5 after the completion of Cohort 4. Cohort 5 will be opened when either Cohort 3 or Cohort 4 is complete. Enrolment in Cohort 5 will continue until 24 evaluable subjects have received RV521 or placebo (2:1). The 4 subjects in the dose group that received the specified dose from each of Cohorts 3 and/or 4 will contribute to this overall total. Thus a minimum of 24 subjects and a maximum of 40 subjects (assuming 2 adjustments per age group) may be enrolled in Part B.

Part C:

Part C will be conducted in a single cohort (Cohorts 6) in subjects ≥ 1 month to ≤ 36 months of age. Subjects will be stratified by age and randomised 1:1:1 to receive one of two dose levels of RV521 or placebo, according to the dose and regimen specified for their age group following

completion of Part B (Cohort 5 subjects) and review of safety/tolerability and pharmacokinetic results from Part B by the DSMC and other selected local regulatory authorities, as required.

8.5.2 Identity of Investigational Products

RV521, a potent small molecule inhibitor of RSV fusion protein mediated cell-cell fusion, and of RSV infection, is formulated as a dry powder blend of RV521 drug substance with mannitol as excipient. The matching placebo is formulated as a dry blend of mannitol and microcrystalline cellulose. The dry blends are filled into hydroxypropyl methylcellulose (hypromellose) capsules.

The RV521 dry powder blend is supplied in 10 mg, 20 mg, and 50 mg RV521 dose strength capsules, expressed as the free base. The composition of the products is stated in Table 8.

Table 8. Composition of RV521 Capsules

Ingredient	RV521 Capsules 10 mg		RV521 Capsules 20 mg		RV521 Capsules 50 mg		Function	Grade
	%w/w	mg/unit	%w/w	mg/unit	%w/w	mg/unit		
RV521 drug substance[1]	6.68	10.82	14.72	21.64	15.24	54.10	Active substance	In-house
Mannitol	93.32	151.18	85.28	125.36	84.76	300.80	Diluent, taste agent	Ph. Eur. / USP / JP
TOTAL	100	162.0	100	147.0	100	354.9	-	-
White, opaque, size 3 HPMC capsule	-	1 per dosage unit	-	1 per dosage unit	-	-	Encapsulation of powder for dispersion	Manufacturer's specification[2]
White, opaque, size 0 HPMC capsule	-	-	-	-	-	1 per dosage unit	Encapsulation of powder for dispersion	Manufacturer's specification[2]

Abbreviations: HPMC = hydroxypropylmethylcellulose, Ph. Eur. = European Pharmacopoeia, USP = United States Pharmacopeia, Ph. JP. = Japanese Pharmacopoeia.

Notes:

1. RV521 drug substance is the hydrochloride salt. The drug product strength is expressed in terms of the free base active moiety. 1.082 g of the hydrochloride salt of RV521 is equivalent to 1.0 g of RV521 free base.
2. HPMC capsules consist of hypromellose of European Commission Regulation (EU) 231/2012, United States 21 Code of Federal Regulations, European Pharmacopoeia (Ph. Eur.), Japanese Pharmacopeia (JP), United States Pharmacopeia (USP)/National Formulary (NF) grade as the structural component and titanium dioxide of EU 231/2012, Ph. Eur., JP, USP/NF grade as an opacifier.

The placebo capsules contain mannitol (85% w/w) and microcrystalline cellulose (15% w/w) of European Pharmacopoeia/United States Pharmacopeia/Japanese Pharmacopeia grade, with overall fill weights for the capsules of 159 mg for the placebo to match 10 mg and 20 mg capsules, and 396 mg for the placebo to match 50 mg capsules.

Capsule shells are white, opaque hydroxypropyl methylcellulose, size 3 for the 10 mg and 20 mg strengths (and matching placebo) and size 0 for the 50 mg strength (and matching placebo).

For the preparation of the dose, the capsules must be opened, and their contents dispersed in a defined volume of permitted suspending diluent prior to oral administration on a mg/kg basis; the capsule shells must not be dispersed into the suspending diluent. Regardless of the suspending diluent to be used for preparing the dose for oral administration, the same process for preparation will be followed. Different dose levels will be attained by using the appropriate combination of capsule strengths, dispersing the contents of the capsules in the correct volume of suspending diluent, then administering the required volume of the resultant dispersion according to the prescribed dose required. Instructions for opening the capsule(s), and dispersing the contents in a fixed volume of suspending diluent prior to administration will be provided in the Pharmacy Manual. Guidance on the permitted suspending diluents will be provided in the Pharmacy Manual.

The IMP will be provided as unblinded kits (RV521) for Part A and blinded kits (RV521 or placebo in accordance with the randomisation schedule) for Parts B and C. A subject will be administered the volume required for the age-range specified dose. In Parts B and C, depending on the weight of the subject, multiple kits of IMP might be assigned to the same subject.

The IMP will be stored under ambient conditions between 15°C and 25°C.

The IMP will be manufactured and imported according to the relevant regulatory requirements.

8.5.3 Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) for Medicinal Products and the relevant regulatory requirements.

8.5.4 Method of Assigning Subjects to Treatment Groups

Part A:

Part A of the study is open-label and all subjects will receive RV521. The dose to be received by a given subject will be the dose currently being investigated, at the time the subject is enrolled, in the applicable cohort, as described in Section 8.

Part B and Part C:

In Parts B and C, subjects will be randomised to treatment according to a central randomised list for each cohort. To protect the blind, the list will be produced by an unblinded biostatistician at Syneos Health who will be independent of the blinded statistician.

For Part B, subjects in Cohorts 3 and 4 will be randomised to RV521 or placebo (3:1). The randomisation list for Cohort 5 will be designed to ensure that the subjects who contribute to the final recruitment total of 24 are randomised to receive RV521 or placebo (2:1). The dose to be received by a given subject will be the dose currently being investigated at the time the subject is enrolled, in the applicable cohort, as described in Section 8.1.

For Part C Cohort 6, the randomisation list will be designed such that the total of approximately 111 subjects (37 subjects per treatment group) will be randomised with an aim to have at least 34 evaluable subjects included in the analysis of viral load. Randomisation will be stratified by age

group (≥ 1month to < 6 months vs. ≥ 6 months to ≤ 36 months) to ensure balance across the treatment groups, but there is no specified number of subjects that will be required in each stratum. Subjects will receive RV521 (age group specific low or high dose level) or placebo in a 1:1:1 ratio. Subjects randomised to placebo will be allocated randomly to either a low dose volume or a high dose volume to maintain the integrity of the double-blind design.

At the time of randomisation, a subject will be sequentially assigned to the next available treatment from the randomisation list for that cohort and stratum. Randomisation will be performed using an interactive web response system (IWRS). A blinded treatment kit (or > 1 kit, if required, in Part B and Part C), corresponding to the randomised treatment, will be allocated to each subject.

8.5.5 Blinding

Part A of the study is open-label assignment to RV521.

Parts B and C of the study are double-blind. All subjects' parents/guardians, Investigators and their designees, and all study personnel involved in the conduct of the study, including data management and biostatistics, will be blinded to treatment assignment.

No blinded team member will have access to the randomisation list before official unblinding of study treatment. The randomisation schedule may be shared with other groups outside of the Syneos Health study team (eg, the pharmacovigilance department, and the laboratory analysing the PK samples).

Data and Listings together with the randomisation list will be provided to DSMC for review for Part B. An unblinded, independent biostatistician will be assigned by Syneos Health to prepare unblinded tables, figures, and listings related to Part C of the study for the DSMC. The unblinded statistician will not otherwise participate in study procedures. **Note**: this could be the same independent biostatistician who produces the randomisation schedule.

Unblinding is discouraged but will be permitted in a medical emergency that requires immediate knowledge of the subject's assigned treatment. Emergency unblinding will only be acceptable if it affects the medical management. If this is the case, it will be done within the IVRS.

8.5.6 Prior and Concomitant Therapy

All prior medication taken within 14 days prior to the study and all concomitant medication taken during the study must be documented in the CRF. The information must include trade and international non-proprietary name of medication, indication, daily dose, route of administration, and start and end date of administration, if applicable, to support accurate coding in accordance with the World Health Organisation (WHO) Drug dictionary.

8.5.6.1 Permitted Medication/Therapy

RV521 is a weak inhibitor of MATE-1. Metformin should be used with caution and glucose levels should be closely monitored.

Medications that are CCI substrates with a narrow therapeutic range (See Appendix 17.3) such as fentanyl that are required, e.g. in patients requiring procedures or ventilation, will be permitted provided that the subjects are appropriately monitored by the investigator who should be aware that the active investigational product (sisunatovir) may compete for the metabolism of such products, resulting in higher drug levels of these medications.

8.5.6.2 Prohibited Medication/Therapy

The following medications/therapy will not be permitted during the study:

- Palivizumab or treatment with any antiviral therapy for RSV (eg, ribavirin or IV immunoglobulin)
- Corticosteroids (oral, IV, or inhaled)
- Heliox
- Leukotriene receptor antagonists (eg, montelukast)
- Exogenous surfactant
- Mucolytics
- Any drug, which could impact on the PK of the investigational product including potent inhibitors or moderate or potent inducers of CYP P450s (for details see Appendix 17.3).
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to CCI, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.
- Consumption of CCI -containing products are not allowed throughout the study. CCI .

Subjects who need to start treatment with prohibited medications during the study will be required to discontinue study treatment, but must remain in the study according to the post-study drug treatment period specified in the Schedule of Assessments, and should also attend the follow-up visit. After the end of their participation in the study, each subject will be treated according to standard clinical practice.

8.5.6.3 Rescue Medication

Not applicable.

8.5.7 Treatment Compliance

Investigational medicinal product will be administered by an appropriately qualified person at the study site. Administration will be documented on the drug accountability sheet, in the subject's medical record, and in the CRF.

When a subject is discharged from hospital and IMP will be administered at home (Parts B and C), the parent/legal guardian (and/or another caregiver, if required) will be trained in the storage, preparation, and administration of IMP at home and will be issued a treatment diary card to record the relevant details of IMP administration. The parent/legal guardian will be instructed how to complete the treatment diary card accurately. Where possible, prior to each dose, a site representative will contact the parent/legal guardian to ensure compliance with the IMP administration procedure.

9 TIMING OF STUDY PROCEDURES

The parent(s) or legal guardian(s) will provide written informed consent before any study-related procedures are performed.

The planned study assessments are presented in the relevant table in Section 8.1.

9.1 Pre-treatment

9.1.1 Screening Visit: Part A, Part B, and Part C (-24 Hours to First Dose)

Ensure the appropriate Informed Consent Form (ICF) was properly executed:

- Written informed consent
- RSV Rapid Diagnostic Test
- Inclusion and exclusion criteria
- Demographics
- Medical history
- Prior medication review
- Physical examination (including a symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Evaluation of hydration status
- Body weight/length/head circumference
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied (Part A only)
- Pulse oximetry on room air (if deemed safe by PI or health care provider) (Part A only)
- 12-Lead ECG
- Record RSV-related signs and symptoms (every 12 hours), date of onset and severity (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing (Parts B and C only)
- ReSVinet Scale for Clinicians (Part C only, Appendix 17.6)
- RSV Clinical Scoring System (Part A and B only; Appendix 17.1)
- Safety laboratory tests (clinical chemistry and haematology)
- Urinalysis
- Adapted ReSVinet scale for parental use (Part B and C only, Appendix 17.2)
- Concomitant medication review
- Adverse event review

Note: All the screening assessments (except the RSV Rapid Diagnostic Test) should be completed within 24 hours before Dose 1. A positive RSV Rapid Diagnostic Test result is required on a sample collected within 48 hours before Dose 1.

9.2 Treatment Period Part A

9.2.1 Dosing (Part A)

Dosing Visit 1:

Pre-Dose (Within 2 Hours of Study Drug Administration):

- Reassess for eligibility against the inclusion and exclusion criteria
- Physical examination (symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Evaluation of hydration status
- Vital signs (body temperature systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula) and percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- 12-Lead ECG
- RSV Clinical Scoring System (Appendix 17.1)
- Nasopharyngeal swab according to the sampling schedule in Table 4
- Concomitant medication review
- Adverse event review

Dosing (0 Hours):

- Study medication administration
- Concomitant medication review
- Adverse event review

1-2 Hours Post-Dose:

- PK blood sample according to the sampling schedule in Table 5

4-5 Hours Post-Dose:

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- PK blood sample according to the sampling schedule in Table 5
- Concomitant medication review
- Adverse event review

6-8 Hours Post-Dose:

- PK blood sample according to the sampling schedule in Table 5
- Concomitant medication review
- Adverse event review

12 Hours Post-Dose:

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- PK blood sample according to the sampling schedule in Table 5
- Optional Nasopharyngeal swab according to the sampling schedule in Table 4
- Concomitant medication review
- Adverse event review

18-24 Hours Post-Dose:

- Physical examination (symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- 12-Lead ECG
- RSV Clinical Scoring System (Appendix 17.1)
- PK blood sample according to sampling schedule in Table 5
- Nasopharyngeal swab according to the sampling schedule in Table 4
- Concomitant medication review
- Adverse event review

9.2.2 Post-Treatment (Part A)

Post Dosing Visit 2 (36 Hours Post-Dose):

- Optional Nasopharyngeal swab according to sampling schedule in Table 4

Post Dosing Visit 2 (48 Hours Post-Dose):

- Physical examination (symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Hydration status
- Body weight/length/head circumference
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- 12-Lead ECG
- RSV Clinical Scoring System (Appendix 17.1)
- Safety laboratory tests (clinical chemistry and haematology)

- Urinalysis
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review

Telephone Follow-Up (Day 7)

- Concomitant medication
- Adverse event review

9.3 Treatment Period Part B

9.3.1 Dosing Visit 1 (Part B)

-2 Hours to 0 Hours Pre-Dose 1:

- Reassess for eligibility against the inclusion and exclusion criteria
- Physical examination (symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- RSV Clinical Scoring System (Appendix 17.1)
- Record RSV-related signs and symptoms and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing.
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Randomisation for eligible subjects

Note: If any of the assessments above were carried out within 2h Pre-Dose 1 for screening purposes, it is not necessary to repeat that assessment for the -2h to 0h Pre-Dose 1 timepoint. However, if the assessment was carried out >2 h prior to Dose 1 for screening purposes (i.e. within the first 22 hours of the screening window), the assessment must be repeated between-2h to 0h Pre-Dose 1.

Dosing (0 Hours):

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Study medication administration
- The times of the prior feeding and first feeding after dosing should be recorded.
- Adverse event review
- Concomitant medication review

1-2 Hours or 4-5 Hours or 6-8 Hours Post-Dose 1:

The following assessments will be carried out at either 1 to 2 hours, 4 to 5 hours or 6 to 8 hours Post-Dose 1. The time point chosen (1-2, 4-5 or 6-8 hours) will be defined after PK analysis of Part A.

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- PK blood sample according to sampling schedule in Table 5
- Concomitant medication review
- Adverse event review

12 Hours Post-Dose 1 (Pre-Dose 2):

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- PK blood sample according to sampling schedule in Table 5.
- Optional Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study medication administration (Dose 2)
- The times of the prior feeding and first feeding after dosing should be recorded.

9.3.2 Dosing Visit 2 (Part B)

Doses 3 and 4:

Pre-Dose 3 and 4:

- Evaluation of hydration status (prior to Dose 3 only)
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG (prior to Dose 3 only)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- RSV Clinical Scoring System every 24 hours (prior to Dose 3 only) (Appendix 17.1)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Nasopharyngeal swab according to sampling schedule in Table 4 (Pre-Dose 4 sample is optional)
- Concomitant medication review

- Adverse event review
- Study medication administration (Dose 3 and Dose 4)
- The times of the prior feeding and first feeding after dosing should be recorded.

9.3.3 Dosing Visit 3 (Part B)

Dose 5:

Pre-Dose 5:

- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Record RSV-related signs and symptoms, and severity every 12 hours (if subject remains hospitalised), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- RSV Clinical Scoring System performed every 24 hours (Appendix 17.1)
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study medication administration (Dose 5)
- The times of the prior feeding and first feeding after dosing should be recorded.

Dose 6:

Pre-Dose to 0 Hours:

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- PK blood sample according to sampling schedule in Table 5
- Nasopharyngeal swab according to the sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study Medication administration (Dose 6)
    - The times of the prior feeding and first feeding after dosing should be recorded.

1-2 Hours OR 4-5 Hours OR 6-8 Hours Post-Dose 6:

The following assessments will be carried out at either 1 to 2 hours, 4 to 5 hours or 6 to 8 hours Post-Dose 6. The time point chosen (1-2, 4-5 or 6-8 hours) will be defined after PK

analysis of Part A and sites will be notified of the chosen time point in the Dosing Guidance letter.

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- PK blood sample according to sampling schedule in Table 5
- Concomitant medication review
- Adverse event review

If a subject is discharged:

The parent/legal guardian (and another caregiver, if required) must be trained on the storage, preparation, and administration of the IMP at home. The parent/legal guardian will be issued with the IMP kit(s) for their child and adequate supplies for preparation and administration of the remaining doses of IMP will be provided. A Treatment Diary Card will be issued that explains how the IMP should be stored and prepared and the parent/legal guardian will be asked to record relevant details of the administration of IMP at home (including date and time). Instructions should also be given on when to return to the clinic for Study Visits.

9.3.4 Dosing Visits 4 and 5 (Part B)

(Doses 7 to 10):

If in-patient:

Pre-Dose 7 to 10:

- Evaluation of hydration status (prior to Doses 7 and 9)
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG (prior to Doses 8 and 10)
- RSV Clinical Scoring System performed every 24 hours (prior to Doses 7 and 9)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing (prior to each dose)
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), percent O_2/flow rate supplied (prior to each dose)
- Pulse oximetry on room air (if deemed safe) by PI or health care provider (prior to each dose)
- PK blood sample 12 hours Post-Dose 6 (pre-Dose 7 only) according to sampling schedule in Table 5
- Nasopharyngeal swab (prior to each dose) according to sampling schedule in Table 4. Pre-Dose 8 and 10 Nasopharyngeal swab samples are optional.
- Concomitant medication review
- Adverse event review
- Study medication administration (Doses 7 to Dose 10)
    - The times of the prior feeding and first feeding after dosing should be recorded.
- In case of discharge: provide parent/legal guardian with treatment diary, patient leaflet, and clear instructions how to administer IMP. An additional nasopharyngeal swab sample

should be taken according to Table 4 if the last nasopharyngeal swab sample was taken > 12 hours prior to the discharge.

9.3.5 Post-Treatment (Part B)

Visit Day 7 (40-48 Hours Post-Dose 10) Follow-Up:

Note: Visit Day 7 may occur on Study Days 7 or 8 depending on when the subject received their first Dose of IMP.

- Physical examination (symptom-directed examination, general condition, lung auscultation, and respiratory muscles retractions)
- Evaluation of hydration status
- Body weight/length/head circumference
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- RSV Clinical Scoring System
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Adapted ReSVinet scale for parental use
- Safety laboratory tests (clinical chemistry and haematology)
- Urinalysis
- PK blood sample according to sampling schedule in Table 5
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review

Telephone Follow-Up (Day 12):

- Concomitant medication review
- Adverse event review

9.4 Treatment Part C

Ideally all subjects in Part C should remain hospitalised for at least 48 hours post-randomisation to accommodate taking the first 4 doses of IMP and collection of all the assessments scheduled for Dosing Visit 1 and Dosing Visit 2 (Table 3a)

A subject may be discharged from hospital prior to Dosing Visit 3 and be seen as an outpatient provided all of the following requirements are met:

1. The subject is judged by the Investigator or other healthcare provider to be doing well clinically and to warrant hospital discharge,
2. The parent/caregiver can comply with the dosing at home,

3. Adequate provisions are in place for the subject to be seen in an outpatient setting to complete the study procedures and assessments, either at the hospital/clinic as an outpatient or at home (ie, visited by a home health nurse or equivalent). For both outpatient settings, the following assessments and sample collections are required for key study endpoints:
    a. Administer one dose per Dosing visit or observe parent caregiver doing the same
    b. Obtain at least one nasopharyngeal swab sample each day (Pre-Dose at Dosing Visits 2, 3 and 4 and 5)
    c. Obtain PK samples Pre-Dose 6, and at 4-5 hours Post-Dose for either Dose 6 or Dose 7 (depending on the time of day for the doses)
    d. Obtain an ECG at Post-Dose 6. Depending on the time of day Dose 6 falls the assessments can be moved relative to Dose 7
    e. Assess the following at each of Dosing Visits 2, 3, 4 and 5
        - Adverse events
        - Concomitant medication review
        - Vital signs
        - Hydration status
        - ReSVinet Score for Clinicians
        - RSV signs and symptoms
        - Supplementary Oxygen
        - Pulse oximetry on room air

Following the outpatient visits on Dosing Visit 3, the parent/caregiver must continue to complete all home dosing and the Adapted ReSVinet scale for parental use assessments on Dosing Visits 4 and 5 as outlined in Table 3b and must return for Visit Day 7 40-48 hours after the last dose (Dose 10), Visit Day 14 and Visit Day 34. The parent/caregiver will record in the Patient Booklet for doses given at home whether any concomitant medications have been administered and also their assessment of how the child is feeling.

9.4.1 Dosing Visit 1 (Part C)

-2 Hours to 0 Hours Pre-Dose 1:

- Reassess for eligibility against the inclusion and exclusion criteria
- Physical examination
- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- ReSVinet Scale for Clinicians (Appendix 17.6)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing

- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Randomisation for Eligible Subjects (stratified by age group)
- Nasopharyngeal swab
- Concomitant medication review
- Adverse Events

Note: If any of the assessments above were carried out within 2 h Pre-Dose 1 for screening purposes, it is not necessary to repeat that assessment for the -2 h to 0 h Pre-Dose 1 timepoint. However, if the assessment was carried out >2 h prior to Dose 1 for screening purposes (i.e. within the first 22 hours of the screening window), the assessment must be repeated between-2 h to 0 h Pre-Dose 1.

Dosing (0 Hours):

- Concomitant medication review
- Adverse event review
- Study medication administration (Dose 1)
    - The times of the prior feeding and first feeding after dosing should be recorded.

+4-5 Hours Post-Dose 1:

The following assessments will be carried out at 4 to 5 hours Post-Dose 1.

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- Concomitant medication review
- Adverse event review
- PK blood sample according to sampling schedule in Table 5. **Note:** This sample will only be required if the dose level was not previously evaluated in Part B.

12 Hours Post-Dose 1 (Pre-Dose 2):

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Optional Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- PK blood sample according to sampling schedule in Table 5. NOTE: This sample will only be required if the dose level was not previously evaluated in Part B.
- Study Medication Administration (Dose 2)

- The times of the prior feeding and first feeding after dosing should be recorded.

9.4.2 Dosing Visit 2 (Part C)

Procedures and assessments scheduled for Dosing Visit 2 in Part C are required if the subject is currently hospitalised. If the subject has met the criteria for early discharge prior to Dosing Visit 2 and is being seen as an outpatient the required assessments should still be completed and are listed in Section 9.4 and Table 3b. In case of early discharge, provide parent with Patient Booklet, video access link and clear instructions how to administer IMP. An additional nasopharyngeal swab sample should be taken according to Table 4 if the last nasopharyngeal swab sample was taken > 12 hours prior to discharge.

Pre-Dose 3:

- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- ReSVinet scale for clinicians (Part C only, Appendix 17.6)
- Adapted ReSVinet scale for parental use (Appendix 17.2)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study Medication Administration (Dose 3)
  - The times of the prior feeding and first feeding after dosing should be recorded.

Pre-Dose 4:

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Record the use of supplemental oxygen, method of delivery (eg nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Optional Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study Medication Administration (Dose 4)
  - The times of the prior feeding and first feeding after dosing should be recorded.

9.4.3 Dosing Visit 3 (Part C)

Procedures and assessments scheduled for Dosing Visit 3 in Part C are required if the subject is currently hospitalised. If the subject has met the criteria for early discharge and is being seen as an outpatient the required assessments are listed in Section 9.4 and Table 3b. In case of early discharge, provide parent with Patient Booklet, video access link and clear instructions how to administer IMP. An additional nasopharyngeal swab sample should be taken according to Table 4 if the last nasopharyngeal swab sample was taken > 12 hours prior to discharge.

Pre-Dose 5 (All of the assessments to be completed if still an in-patient):

- Evaluation of hydration status
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- ReSVinet scale for clinicians (Appendix 17.6)
- Adapted ReSVinet scale for parental use (Appendix 17.2)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study Medication Administration (Dose 5)
    - The times of the prior feeding and first feeding after dosing should be recorded.

Dose 6 (All of the assessments to be completed if still an in-patient)

Pre-Dose to 0 Hour:

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- Record RSV-related signs and symptoms, and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- Record the use of supplemental oxygen, method of delivery (eg, nasal cannula), Percent O_2/Flow rate supplied
- Pulse oximetry on room air (if deemed safe by PI or health care provider)
- PK blood sample according to sampling schedule in Table 5
- Nasopharyngeal swab according to sampling schedule in Table 4
- Concomitant medication review
- Adverse event review
- Study Medication Administration (Dose 6)
    - The times of the prior feeding and first feeding after dosing should be recorded.

+4-5 Hour Post-Dose 6:

The following assessments will be carried out at 4 to 5 hours Post-Dose 6.

- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- PK blood sample according to sampling schedule in Table 5
- Concomitant medication review
- Adverse event review

If a subject is discharged:

The parent/legal guardian (and another caregiver, if required) must be trained on the storage, preparation, and administration of the IMP at home. The parent/legal guardian will be issued with the IMP kit(s) for their child and adequate supplies for preparation and administration of the remaining doses of IMP will be provided. A Patient Booklet and video access link will be issued that explains how the IMP should be stored and prepared and the parent/legal guardian will be asked to record relevant details of the administration of IMP at home (including date and time). Instructions should also be given on when to return to the clinic for Study Visits.

See Section 9.4 and Table 3b for details of assessments required in subjects who are outpatients.

9.4.4 Dosing Visits 4 and 5 (Part C)

(Doses 7 to 10) - All of the assessments to be completed if still an in-patient:

- Evaluation of hydration status (Doses 7 and 9)
- Vital signs (body temperature, systolic and diastolic BP, HR, RR) (prior to each dose)
- 12-Lead ECG (prior to Doses 8 and 10)
- ReSVinet scale for clinicians every 24 hours (Doses 7 and 9) (Appendix 17.6)
- Adapted ReSVinet scale for parental use (Appendix 17.2). **Note**: To be completed whether hospitalised or discharged.
- Record RSV-related signs and symptoms and severity every 12 hours (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing (prior to each dose)
- Record the use of supplemental oxygen , method of delivery (eg, nasal cannula), percent O_2/flow rate supplied (prior to each dose)
- Pulse oximetry on room air (if deemed safe by PI or health care provider (prior to each dose)
- Nasopharyngeal swab according to sampling schedule in Table 4. Pre-Dose 8 and 10 Nasopharyngeal swab samples are optional.
- Concomitant medication review
- Adverse event review
- PK blood sample according to sampling scheduled in Table 5. **Note**: This sample will only be required if the dose level was not previously evaluated in Part B.
- Study medication administration (Dose 7 to Dose 10), whether hospitalised or discharged
    - The times of the prior feeding and first feeding after dosing should be recorded.

- In case of discharge: provide parent with Patient Booklet, video access link, and clear instructions how to administer IMP. An additional nasopharyngeal swab sample should be taken according to Table 4 if the last nasopharyngeal swab sample was taken > 12 hours prior to discharge.

9.4.5 Post Treatment (Part C)

Visit Day 7 (40 – 48 Hours Post-Dose 10) Follow-up:

Note: Visit Day 7 may occur on Study Days 7 or 8 depending on when the subject received his or her first dose of IMP.

- Physical examination
- Evaluation of hydration status
- Body weight/length/head circumference
- Vital signs (body temperature, systolic and diastolic BP, HR, RR)
- 12-Lead ECG
- Record RSV-related signs and symptoms, and severity (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- ReSVinet scale for clinicians (Appendix 17.6)
- Adapted ReSVinet Scale for Parental use (Appendix 17.2)
- Safety laboratory tests (clinical chemistry and haematology)
- Urinalysis
- PK blood sample according to sampling schedule in Table 5
- Nasopharyngeal swab
- Concomitant medication review
- Adverse event review

Visit Day 14 Follow-up:

- Vital signs
- Body weight/length/head circumference
- Record RSV-related signs and symptoms, and severity (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing
- ReSVinet scale for clinicians (Appendix 17.6)
- Adapted ReSVinet scale for parental use (Appendix 17.2)
- Nasopharyngeal swab
- Concomitant medication review
- Adverse event review

Visit Day 34 Follow-up:

- Vital signs
- Body weight/length/head circumference
- Record RSV-related signs and symptoms, and severity (if indicated), including: temperature, cough, coryza, grunting with expiration, nasal flaring, retractions, and wheezing

- ReSVinet scale for clinicians (Appendix 17.6)
- Adapted ReSVinet scale for parental use (Appendix 17.2)
- Nasopharyngeal swab
- Concomitant medication review
- Adverse event review

Early Withdrawal (or Discontinuation) Visit

Parents/legal guardians who withdraw their child from the study will be encouraged to allow their child to complete the same final evaluations as subjects completing the study according to this protocol (ie, at the relevant post-treatment visit), particularly safety evaluations.

9.5 Duration of Treatment

Part A:

Subjects will participate for up to 8 days. A single oral dose of RV521 will be administered in Part A, and the visit schedule will include:

- Screening Visit (-24 hours)
- Dosing Visit 1 (-2 pre-dose to 18-24 hours post-dose)
- Post-dosing Visit 2 (48 hours post-dose)
- Telephone Follow-up (Day 7)

Part B:

Subjects will participate for up to 13 days. The proposed dosing regimen for Part B is RV521 or placebo administered BID, 12 hours apart, for a period of 5 consecutive days (for a total of 10 doses), and the visit schedule will include:

- Screening Visit (-24 hours)
- Dosing Visit 1 (-2 to 18-24 hours post-dose)
- Dosing Visit 2
- Dosing Visit 3
- Dosing Visit 4
- Dosing Visit 5
- Follow-Up Visit Day 7 (+40-48 Hours Post-Dose 10)
- Telephone Follow-Up (Day 12)

Note: The actual day of each Dosing Visit will be dependent upon the time that the subject receives their first dose of IMP on Visit 1. Follow-Up Visit Day 7 may therefore fall on Study Days 7 or Day 8 depending upon the time the subject received his or her first dose of IMP on Dosing Visit 1.

Part C:

Subjects will participate for up to 35 days, and the visit schedule will include: Screening (24 hours to first dose), Dosing Visits 1 to 5 (5 days), and follow-up 40-48h Post-Dose 10 (Study

Days 7 or 8) and at Study Days 14 and 34. Inpatient duration will be determined clinically by the PI or other health care provider and by ability to complete study procedures and assessments on an outpatient basis (Section 9.4). Follow-up days are expected to be on an outpatient basis.

10 PHARMACOKINETICS, EFFICACY AND SAFETY VARIABLES

The planned Schedule of Assessments is in Section 8.1.

The intended volume of blood to be withdrawn for each of the assessments is based on the minimal, reasonably required volume for each of the respective analyses and is below those allowed per the WHO and European and United States guidance.

In order to limit the volume of blood to be collected, the normal protocol-driven tests will only be performed within the indicated time frame as part of the standard of care.

For safety tests (haematology and chemistry), a total of 4.2 mL of blood will be drawn, per protocol (all study parts).

For PK analysis, 0.2 mL of whole blood is required at each sampling time point. Thus, for a maximum of 6 PK samples (Part B), 1.2 mL of whole blood will be required.

The maximum amount of blood that will be taken for the study will be 5.4 mL.

Collection schedules may switch between the cannulation and heel prick methods dependent upon the presence and availability of a patent IV cannula as well as the sample purpose (PK versus safety evaluations).

Complete instructions for collection, processing, handling, and shipment of all safety laboratory tests, PK, and nasopharyngeal swab samples will be provided in the Laboratory Manual.

10.1 Pharmacokinetics, Efficacy, and Safety Assessments

10.1.1 Pharmacokinetic Assessments

Blood samples for measurement of serum concentrations of RV521 will be drawn at time points specified in the Schedule of Assessments in Section 8.1. The actual date and time (24-hour clock time) of each sampling will be recorded in the subject's source document at the site. The sampling window for each time point is identified in Table 1, Table 2, and Table 5. Plasma samples for determination of RV521 concentrations will be analysed by a central laboratory using a validated assay method. Full details of the analytical methods used will be described in a separate bioanalytical report. Deviations from planned sampling windows will be assessed before database lock for the impact on PK analyses and may be excluded from time point summaries of PK concentrations. Actual time will be used for derivation of PK parameters.

If a subject experiences an AE Grade 3 or higher or meets SAE criteria, a blood sample for the measurement of serum concentrations of RV521 should be collected (if less than 24 hours have elapsed since the last dose of IMP and more than 24 hours since the last PK sample), if possible. The sample will be recorded as an unscheduled time point and may be also used in PK parameters derivation using actual time.

10.1.2 Efficacy Assessments

10.1.2.1 Viral Load Assessments

A single nasopharyngeal swab sample for the measurement of RSV viral load will be taken at each time point identified in the Schedule of Assessments for Part A (Table 1), Part B (Table 2), and Part C (Table 3a inpatients and Table 3b outpatients) in Section 8.1. The actual date and time (24-hour clock time) of each sampling will be recorded in the subject's source document at the site. Deviations from planned sampling windows will be assessed before database lock for the impact on PD analyses. Actual time will be used for derivation of PD parameters.

Cell-based infectivity assay and RT-qPCR assay will be used to quantify RSV viral load in nasopharyngeal swab samples. CCI [redacted]

[redacted]

10.1.2.2 Clinical Response Assessments

Clinical response will be measured by evaluation of the RSV signs and symptoms list (all Parts), RSV Clinical Scoring System (Parts A and B), the ReSVinet Score for Clinicians (Part C), and the adapted version of ReSVinet scale for parental use (Parts B and C). In addition, CCI [redacted] and time to normalisation of respiratory rate will be analysed in Part C. Details of how the clinical efficacy endpoints will be analysed, and by which scales, is briefly described in Section 11.1.5 and will be outlined in the Statistical Analysis Plan.

10.1.3 Safety Assessments

Safety assessments will consist of AEs, haematology, clinical chemistry, urinalysis, vital signs, physical examination, and ECGs.

10.1.3.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the

CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the Investigator to document all AEs that occur during the study from the time the ICF is signed. AEs and SAEs should be followed until resolution or until the event is stable. An AE should be reported on the appropriate page of the CRF.

Each separate AE episode must be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this must be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

Adverse Reaction Definition

An adverse reaction is any untoward and unintended response that is related to the administration of the IMP at any dose.

Onset Date, End Date

If an AE starts during the study but did not end before the final closing (follow-up) visit, the Investigator must make a reasonable effort to establish the outcome and the end date of the AE. If this is not possible (eg, because the AE is still ongoing) or the subject is lost to follow-up, there will be no end date for the AE.

For all AEs that resolve, resolve with sequelae, or have a fatal outcome, an end date must be provided.

If an AE stops and restarts later, all occurrences have to be recorded separately.

Assessment of Severity

Severity of AEs will be assessed by the Investigator using NCI CTCAE v5.0, 27 November 2017 (CTCAE v5.0). Grades of the NCI CTCAE refer to the severity of the AE as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

If there is a change in severity of an AE, every episode of the AE will be captured separately and all required information for every episode will be provided separately.

Assessment of Causality

Every effort will be made by the Investigator to assess the relationship of the AE, if any, to the IMP. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP.
Unlikely:	Clinical event whose time relationship to IMP makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possibly:	Clinical event with a reasonable time relationship to IMP, but that could also be explained by concurrent disease or other drugs or chemicals.
Probably:	Clinical event with a reasonable time relationship to IMP, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Definitely:	Clinical event with plausible time relationship to IMP, and that cannot be explained by concurrent disease or other drugs or chemicals.

Action Taken with IMP

The Investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None (no action taken)
- Unknown
- IMP temporarily interrupted – only for Part B and Part C (date, time and reason to be provided)
- IMP permanently discontinued (date and reason to be provided)
- Other (to be specified)

Outcome of Adverse Event

The final outcome of the AE will be documented in the appropriate section of the eCRF, as follows:

- Recovered
- Recovered with Sequelae
- Ongoing
- Unknown
- Death

Follow-up of Adverse Events

All Investigators should follow up subjects with AEs or SAEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilised or determined to be chronic. Details of AE or SAE resolution must be documented in the CRF.

Subjects should be followed up to the last follow-up visit, (ie, Day 7 after receiving the last dose of IMP in Part A, Day 12 in Part B, and Day 34 in Part C) and any AEs that occur during this time should be reported according to the procedures outlined above.

For all SAEs, where important or relevant information is missing, active follow-up should be undertaken.

A follow-up report must be completed when an SAE resolves, is unlikely to change, or when additional information becomes available. In case the SAE is a suspected unexpected serious adverse reaction (SUSAR), follow-up information must be provided within the timelines as requested by Syneos Health Safety & Pharmacovigilance.

If new or amended information on a reported SAE becomes available, the Investigator can report this on a new SAE form using the completion guidelines. If using the original form to notify further information, all new or amended information need to be initialled and dated in order all changes are clearly identified.

Documentation and Reporting of Adverse Events

An AE should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages.
The following data should be documented for each AE:

- Diagnosis, if not available, symptoms
- Classification of ‘serious’ or ‘not serious’
- Severity
- Date and time of first occurrence and date and time of resolution (if applicable)
- Action taken with the IMP
- Causal relationship
- Outcome of event (unknown, recovered, ongoing, recovered with sequelae, death [with date, time, and cause reported])

10.1.3.2 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form)
- Requires or prolongs inpatient hospitalisation. (Complications occurring during hospitalisation are AEs and are SAEs if they cause prolongation of the current hospitalisation. Hospitalisation / Prolonged hospitalisation for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalisations must be recorded on the medical history or physical examination page of the CRF)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions)

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardised the subject or required intervention to prevent 1 of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

Any SAE must be reported by the Investigator if it occurs during the clinical study from signature of Informed Consent through to the last scheduled Study Visit, whether or not the SAE is considered to be related to the IMP. If an AE becomes an SAE, the start date of the SAE is the date that the AE fulfils any seriousness criterion. The stop date of an SAE is the date that the event resolves or no longer fulfills the seriousness criterion.

An SAE report consists of the SAE form. SAE reports should be sent **within 24 hours** by e-mail to the Syneos Health Safety and Pharmacovigilance department:

SafetyReporting@SyneosHealth.com [redacted]

The Investigator will be requested to supply as much detailed information regarding the event that is available at the time of the initial report (examinations carried out, laboratory results etc.).

The Investigator is also required to submit follow-up reports as soon as possible, and within 24 hours of becoming aware of any additional information such as diagnosis, outcome, causality assessment, results of specific investigations and any new significant information that has not been previously reported.

The Investigator should not wait to receive additional information to document fully the event before notification of an SAE, although additional information may be requested by the Syneos Health pharmacovigilance department. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of IMP administration and linked by the Investigator to this study, should be reported to the study monitor.

Syneos Health, on behalf of the Sponsor will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favourable opinion of the study. In addition, Syneos Health, on behalf of the Sponsor, will expedite the reporting to all concerned Investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected according to local safety reporting requirements.

10.1.3.3 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the IMP at any dose that is not consistent with the applicable RSI (eg, [IB] for an unauthorised IMP or summary of product characteristics for an authorised product). The expectedness of an adverse reaction is determined by the Sponsor in the RSI.

For this protocol, the RSI for the assessment of expectedness is included in the most recent fully approved version of the IB for RV521.

All SUSARs will be the subject of expedited reporting. Syneos Health shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB, within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days and/or according to local safety reporting requirements. All other SUSARs will be reported to the

relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case and/or according to local safety reporting requirements. All Investigators should follow up SUSARs until the event is resolved or until, in the opinion of the Investigator, the event is stabilised or determined to be chronic. Post-study SUSARs that occur after the subject has completed the clinical study must be reported by the Investigator to the Sponsor.

Warnings and Precautions

Please refer to the IB for RV521 (summary of data, reference safety information, and guidance for the Investigator).

10.1.3.4 Clinical Laboratory Assessments

The following laboratory safety tests will be performed according to the relevant Schedule of Assessments for Part A (Table 1), Part B (Table 2), and Part C (Table 3a inpatients and Table 3b outpatients) in Section 8.1. Clinically significantly abnormal laboratory finding should be followed up until resolution or until the analyte is stable. If the post-treatment data is reported as invalid, an unscheduled visit should be performed to repeat the laboratory safety tests within 2 weeks after Dose 10.

Haematology

Haemoglobin, haematocrit, white blood cell count (total and differential), red blood cell count, platelet count, mean cell volume (MCV), mean cell haemoglobin (MCH), and MCH concentration (MCHC).

Clinical Chemistry

Creatinine, urea (or blood urea nitrogen), AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, and calcium.

Note: for the Screening Visit ONLY, AST and ALT analysis can also be conducted at the local laboratory, although a blood sample must also be sent to the Central laboratory for analysis.

Urinalysis

pH, glucose, ketones, blood, protein, and microscopy.

10.1.3.5 Clinical Laboratory Evaluation

The haematology and clinical chemistry safety laboratory analyses will be performed at the following laboratory:

Eurofins Central Laboratory Lancaster
2430 New Holland Pike
Lancaster, PA 17601
USA
Tel +1 717 556 7350
Fax +1 717 556 3888

For those analyses that are subcontracted to other laboratories (plasma PK and nasopharyngeal swab samples), the test results will be reported directly to Syneos Health.

Reference ranges will be supplied by Eurofins and used by the Investigator to assess the safety laboratory data for clinical significance and pathological changes.

10.1.3.6 Other Laboratory Variables

Not applicable

10.1.3.7 Vital Signs

Vital signs (body temperature, systolic and diastolic BP, oxygen saturation, HR, RR, and pulse oximetry) will be recorded at the time points specified in the relevant Schedule of Assessments for Part A (Table 1), Part B (Table 2) and Part C (Table 3a inpatients and Table 3b outpatients).

In Part C, collected vital signs and SpO_2 levels will be analyzed as normal, mild, moderate, or severe according to the following definitions:

- Temperature:
  - Normal (no fever): <38°C
  - Mild: 38-39°C
  - Moderate: >39-40°C
  - Severe: >40°C
- Respiratory rate (breaths/min):
  - Normal: ≤30
  - Mild: 31-45
  - Moderate: 46-60
  - Severe: >60
- SpO_2 on Room Air (Oxygen Saturation)
  - Normal: >94%
  - Mild: >92-94%
  - Moderate: 90-92%
  - Severe: <90%

10.1.3.8 Physical Examination

A full body physical examination will be performed at the time points specified in the relevant Schedule of Assessments for Part A (Table 1), Part B (Table 2) and Part C (Table 3a inpatients and Table 3b outpatients) in Section 8.1 and will include lung auscultation (wheezing during expiration/inspiration, crackles/crepitations), retraction of respiratory muscles, and general condition. Any changes from baseline will be recorded.

10.1.3.9 Electrocardiograms

A 12-lead ECG will be performed at Screening. Additional 12 lead ECGs will be performed at scheduled time points as indicated in the relevant Schedule of Assessments for Part A (Table 1), Part B (Table 2), and Part C (Table 3a inpatients and Table 3b outpatients) in Section 8.1.

10.1.3.10 Other Evaluations

Pulse Oximetry: Pulse Oximetry should be measured for all subjects without oxygen supply if deemed safe. When the SpO_2 is measured, always record the method of O_2 delivery, even if the SpO_2 is measured on room air. Any changes from baseline will be recorded.

Hydration Status: An evaluation of signs of dehydration according to the judgement of the Investigator should be performed (Appendix 17.5 is to be used for reference) and recorded.

10.2 Data Safety Monitoring Committee

The DSMC will consist of medical advisers/monitors, pharmacokineticists, and biostatisticians. The DSMC will only include independent reviewers.

The DSMC will review all available safety and PK data collected

The specific responsibilities, composition of the DSMC, and the details of outputs provided for the review meeting are outlined in the DSMC Charter.

10.3 Appropriateness of Measurements

Assessments of the safety, efficacy, and PK measures planned for this study are widely used and generally recognised as reliable, accurate, and relevant to the disease condition.

11 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared by Syneos Health as a separate document. The SAP will include a more detailed description of the planned statistical methodologies for each part of the study. The SAP will be finalised before the closure of Part A. Any subsequent SAP amendments applicable to Parts B or C will be signed off prior to database lock and unblinding of the respective parts.

11.1.1 Datasets or Populations Analysed

The study populations include the Safety Population, PK Population, PD Population, and Efficacy Population.

Safety Population: defined as all subjects who received a single dose (Part A) or any part of any multiple dosing regimens (Parts B and C) of IMP (RV521 or placebo). The Safety Population is the primary population for the analysis of safety data. Analysis will be according to actual treatment received.

PK Population: defined as all subjects who receive IMP and have at least 1 post-dose PK concentration measured. The PK Population is the primary population for the analysis of PK data. Analysis will be according to actual treatment received.

Modified Intent-to-Treat (mITT) Population

The mITT Population is the primary population for the analysis of efficacy and PD data. Subjects will be analysed according to the randomised treatment. The mITT Population is defined as follows:

- In Part A, the mITT is defined as all subjects enrolled in the study who have an RT-qPCR viral load measurement and/or CBIA, if available, for at least 1 time point including baseline: pre-dose at Dosing Visit 1.

- In Part B, the mITT Population will include all subjects who received at least one dose of IMP (RV521 or placebo) and have a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during the blind data review meeting. Potential inclusion of subjects who have not completed at least 6 doses of IMP will be decided by the project team during the blind data review meeting. Subjects will be analysed according to the randomised treatment.

- In Part C, the mITT Population will include all subjects who received at least one dose of IMP and have a pre-treatment positive RSV confirmed by the central laboratory.

Demographic and Other Baseline Characteristics: Demographic and baseline characteristics will be summarised descriptively by treatment. Quantitative variables will be summarised using the statistics n (number of observations), mean, standard deviation, median, minimum and

maximum. Qualitative variables will be summarised using n (number of subjects), absolute numbers and relative frequencies (%) per class.

11.1.2 Pharmacokinetic Variables

The PK characteristics of RV521 to be assessed will be: C_{max}, $AUC_{0\text{-}12}$, $AUC_{0\text{-}t}$, $t_{1/2}$, $AUC_{0\text{-}\infty}$, CL/F), V/F and C_{12} (data permitting), and in addition for Part B: accumulation ratio, percent fluctuation, AUC_{tau}, C_{ave}, C_{min} (C_{trough}) as well as any other relevant parameters.

Pharmacokinetic analysis will include listings and summaries of PK concentrations by time point, derived PK, parameters and analysis of relationship with dose and body weight.

Data regarding exposure after accumulation will be compared to parameters observed in adult subjects (C_{max}, AUC_{tau}, C_{12} [data permitting]) with the application of a possible safety factor.

11.1.3 Pharmacodynamic Variables

Pharmacodynamic variables include individual viral loads (by RT-qPCR) and/or CBIA if available at each sampling time point, percent change from baseline for 60 and 156 hours after first dose as well as other additional PD parameters may be also considered as PD endpoints.

For Parts B and C, the DAVG statistic (time-weighted average change in RSV viral load), for both total RSV viral load by RT-qPCR and RSV viral load by CBIA, will be calculated as:

$$\text{DAVG} = \frac{\sum_{i=a}^{b} 0.5\,(Y_i + Y_{i+1})\,(t_{i+1} - t_i)}{t_b - t_a}$$

Where Y_i is the change from baseline in $\log_{10}$ RSV viral load at time point i, *t* is the actual time at the specified time point, *a* is the baseline assessment at Dosing Visit 1, and *b* is the last assessment on Follow up Day 7.

Pharmacodynamic parameters, including the viral load, AUC, and any other PD parameters which are derived, will be summarised by treatment (dose level). For Parts B and C, comparisons will be made between RV521 and placebo using analysis of covariance models. Data will be log transformed as appropriate.

The primary analysis in Part C will be the time-weighted average change in nasopharyngeal RSV viral load which will be calculated from baseline (Day of Randomisation) to Day 7 and compared across treatment groups. An analysis of the RSV viral load in the presence and absence of other known respiratory pathogens will be performed. This analysis will be outlined in the SAP.

Secondary virology endpoints derived from the RSV viral load as measured in nasopharyngeal swabs will include but are not limited to:

- Change from baseline in viral load (RT-qPCR and CBIA) at each time point
- Time to below viral load quantification limit (RT-qPCR and CBIA)

- Proportion of subjects with viral load below quantification limit (RT-qPCR and CBIA) at each timepoint throughout the study

CCI [redacted]

Note: the key analysis will pool subjects with both RSV A and RSV B. However, selected analyses will be repeated for the RSV A and RSV B subgroups separately.

Further details of the analyses will be provided in the SAP.

11.1.4 CCI [redacted]

[redacted]

11.1.5 Clinical Response Variables

Two scales of clinical response will be considered, the RSV Clinical Scoring System and the ReSViNet scale. In Parts A and B, clinicians will complete the RSV Clinical Scoring System, which gives a score from 0 to 12. In Part C, the ReSVinet scale for clinicians, which gives a score from 0 to 20 will be completed. For parental assessment of clinical response, the Adapted Version of ReSVinet Scale for Parental Use, which gives a score from 0 to 20 will be analysed.

Both the RSV Clinical Scoring System and the ReSViNet scale for clinicians will be summarised by treatment (dose level) and time point. In addition, for post-dose assessments, change from baseline will also be summarised, where baseline is the last non-missing score prior to the first dose of study drug. For Parts B and C, comparisons will be made between RV521 and placebo using analysis of covariance models.

In addition the score for the RSV Clinical Scoring System will be categorised as:

- Mild – scores ≤ 5
- Moderate – scores > 5 and < 9
- Severe – scores ≥ 9

The number and percent of subjects with mild, moderate and severe assessments will be summarised by treatment (dose level and time point).

The Adapted Version of ReSVinet Scale for Parental Use score will be summarised by treatment (dose level) and time point. In addition, for post-dose assessments, change from baseline will also be summarised, where baseline is the last non-missing score prior to the first dose of study drug. For Part B and Part C, comparisons will be made between RV521 and placebo using analysis of covariance models.

Individual RSV-related signs and symptoms (Appendix 17.4) at each visit will be summarised by treatment (dose level). Quantitative variables will be summarised using the statistics number of observations (n), mean, SD, median, minimum and maximum values. In addition, change from baseline will also be summarised for post-baseline visits. Baseline will be defined as the last non-missing result before the first dose of study medication. Qualitative variables will be summarised using n (number of subjects), absolute numbers and relative frequencies (%) per class.

Time to improvement will be calculated for RSV-related signs and symptoms that are classified as moderate or severe during the course of the study and will be defined as the time from randomisation until no longer present (absent) or mild.

The Overall Time to Improvement will be defined as the time from randomisation to the time that all RSV-related signs and symptoms are mild or absent. The overall time to improvement will be summarised for each treatment group by mean, median, SD, minimum and maximum and 95% confidence intervals.

Overall Time to Resolution of RSV-related signs and symptoms will be calculated from the time of randomisation to the time that they are no longer present (absent), and will be summarised and analysed as for Time to Improvement.

Treatment groups will be compared for differences in overall severity assessed by the composite symptom score on each day whilst hospitalised and at follow-up visits.

For Part C, time to resolution of symptoms will be compared between each dose level of RV521 and Placebo using a generalised Wilcoxon Rank test. Details of the analysis will be provided in the SAP.

11.1.6 Safety Variables

Adverse events will be coded according to the current version of MedDRA. Summary tables of AEs will be based on TEAEs, defined as events starting, or worsening, after the first dose of IMP. Summaries, by MedDRA SOC and Preferred Term, will be provided for all TEAEs, all treatment-related TEAEs (with causality assessed as possibly, probably or definitively related to IMP), all serious TEAEs and all AEs leading to early discontinuation from the study. Summary tables by maximum severity and maximum relationship, and by intensity per CTCAE will be presented.

For laboratory tests, ECG measures and vital signs parameters, baseline will be defined as the last non-missing result prior to the first dose of IMP. Results at each visit will be summarised using the statistics: n (number of observations), mean, SD, median, minimum and maximum. In addition, change from baseline from all safety parameters will also be summarised by post-baseline visits.

11.1.7 Interim Analyses

No formal interim analyses will be conducted. Each of Parts A, B and C will be reported separately and no pooling of Parts will occur.

Following review of Part B, a decision will be made regarding the dose levels to be investigated in Part C.

Note: Part C data will be analysed separately to the Part B data. Data will not be combined across Parts B and C, and therefore, the analysis of Part B has no impact on the type I error.

11.2 Determination of Sample Size

Because of the exploratory nature of the study, a formal sample size calculation has not been performed for Parts A and B. Twenty-four subjects enrolled in Part B and receiving RV521 or placebo (2:1) at the same dose level and according to the same dosing regimen for their specified age range group are expected to be sufficient to assess safety, PK, and antiviral data.

For an anti-viral effect (Part B), measured as a difference in viral load at a specific time point, and using data from the human challenge model (Study CCI), 24 subjects split 16/8 would have 69% power to identify a difference of 2 log units, 87% power for a difference of 2.5 log units and 96% power for a difference of 3 log units.

Estimates for total enrolment into Part C are based on the report by Cunningham et al (2021); an assumed time-weighted average change in RSV $\log_{10}$ viral load from baseline to day 7 in the placebo group of -1.5 $\log_{10}$ vp/ml, with a standard deviation of 1.25. A sample size of 34 per group will provide 90% power to detect at least 1 $\log_{10}$ decrease in RV521 groups using a 2-sided significance level of 0.05. To account for potential drop outs, an additional 10% will be added to give group size of 37 (total 111 subjects randomised 1:1:1; 2 dose levels of RV-521 vs. placebo).

11.3 Protocol Deviations

Protocol deviations will be listed only. Protocol deviations will be identified through a review of derivations captured by the Syneos Health site monitors and through programmatic checks on the database.

Protocol deviations include:

- Subjects not meeting eligibility criteria.
- Subjects who have been unblinded.
- Subjects taking prohibited concomitant medications during the study.

Further details will be given in the SAP.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centres and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded on a CRF. Data collection must be completed for each subject who signs an ICF and is administered IMP.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable. Appropriate modifications to study conduct, including monitoring and source document verification procedures will be observed, consistent with the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic; March 2020; the EMA Guidance on the Management of Clinical Trials During the COVID-19 (CORONAVIRUS) Pandemic; Version 4 (04/02/2021); and other local guidance in place at the time of study conduct.

The Investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

12.3 Data Management and Coding

Syneos Health will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of Syneos Health.

Study centres will enter data directly into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the electronic case report form (eCRF) must be verifiable against source documents at the study centre. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for prior and concomitant diseases, and AEs, and WHODrug for medications.

Missing or inconsistent data will be noted within the EDC system and queried with the Investigator for clarification. Subsequent modifications to the database will be documented.

12.4 Quality Management and Risk Evaluation

Details are provided in Section 8.3.2.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

On receipt of the IMP, the Investigator (or designee) will conduct an inventory and verify that IMP supplies have been received intact and in the correct amounts before completing the supplies receipt. The Investigator will retain a copy of this receipt at the study centre and send the original receipt to the study monitor. The monitor may check the study supplies at each study centre at any time during the study.

It is the responsibility of the study monitor to ensure that the Investigator (or designee) has correctly documented the amount of the IMP received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study centre at all times. The study monitor will arrange collection of unused IMP returned by the subject's parents/legal guardians. The study monitor will also perform an inventory of IMP at the close-out visit to the study centre. All discrepancies must be accounted for and documented.

13.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and the Sponsor.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study centre, the protocol, the ICF, other written material given to the subject's parent (legal guardian), and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study centre can be initiated or the IMP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The Investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The Investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before the parent(s)/legal guardian(s) have given written informed consent for their child to participate in the study.

The Investigator or designated personnel will inform the parent(s)/legal guardian(s) of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The parent(s)/legal guardian(s) should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the parent(s)/legal guardian(s) will be given ample time to consider the study. The parent(s)/legal guardian(s) will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's study file. A

signed and dated copy of the subject ICF will be provided to the subject's authorised representative.

It should be emphasised that the parent(s)/legal guardian(s) may refuse permission for their child to enter the study or may withdraw their child from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Children of parents(s)/legal guardian(s) who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the willingness of the subject's parent(s)/legal guardian(s) to allow continuation of their child's participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The parent(s)/legal guardian(s) of the study subjects will be informed about this new information and reconsent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorised agents of the Sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, as well as that of any other applicable agency, will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study is defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor or its representatives to inform the study centre when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the Investigator(s). Published data must not compromise the objectives of the study. Data from individual study centres in multicentre studies must not be published separately.

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17 APPENDICES

17.1 RSV Clinical Scoring System for Infants with RSV Infection ≥ 1 Month of Age (Parts A and B)

Score	Respiratory Rate (breaths/min)	Wheezing	Retraction of Respiratory Muscles	General Condition
0	< 30	None[a]	None	Normal
1	31-45	Terminal expiration or only with stethoscope	Intercostal only	-
2	46-60	Entire expiration or audible on expiration without stethoscope	Tracheosternal	-
3	> 60	Expiration and inspiration audible without stethoscope	Severe with nasal flaring	Irritable, lethargic, poor feeding

[a] If no wheezing is audible due to minimal air entry, score 3.

Severity Grading	
≤ 5	Mild
> 5 but < 9	Moderate
≥ 9	Severe

Reference

Wang EE, 1992

17.2 ReSVinet Scale for Parental Use

	Item	0 points	1 points	2 points	3 points
1	Feeding intolerance	No	**Mild** Decreased appetite (the child did not eat the same as normally) and/or presented isolated vomits with or without cough.	**Partial** Frequent vomits with cough, but the child does not vomit with every intake. Feeding exhausts the child.	**Total** Child is unable to feed him/herself. The use of a nasogastric tube or parenteral nutrition was required.
2	Medical intervention	No	**Basic** The child's respiratory secretions required removal, he or she was explored by a physician or received sporadically nebulised medication. Antipyretics were administered.	**Intermediate** The child required oxygen therapy, underwent a chest X-ray exploration, or a blood sample was extracted. Treatment with nebulised drugs was given regularly.	**High** The child required respiratory support with a machine. Respiratory support was given through a special mask applied on the nose or mouth or resting on the child's face, or through an endotracheal tube.
3	Respiratory difficulty	No	**Mild** The child was not breathing normally, but he/she does not seem to have any difficulty when drawing air.	**Moderate** The child made an effort for breathing. Respiratory noises can be heard without the need of a stethoscope (just approaching the ear to his or her chest).	**Severe** Respiratory effort was obvious. The child made important movement of his/her chest, the chest even collapses with every movement, and muscles of neck and belly were used. A lot of respiratory noise was heard without approaching the ear to the child's chest.
4	Respiratory frequency	Normal	**Mild or occasional tachypnoea** The child breathed more rapidly, but the situation was well tolerated, or the respiratory frequency was normalised after removing secretions from respiratory airways or administering nebulised medication.	**Prolonged or recurrent tachypnoea** The child breathed more rapidly in a more persistent manner, even after receiving nebulised medication or removing secretions from respiratory tract.	**Severe alteration** The child breathed quickly and superficially, or really deeply. The child was agitated or drowsy.
5	Apnoea	No			Yes The child stopped breathing. It may have been necessary to stimulate him/her in order to regain normal breathing rate.
6	General Condition	Normal	**Mild** Child did not seem the same as always, but there did not seem to be anything to worry about.	**Moderate** Child looked ill, and medical examination was required, but it did not feel like a life-threatening situation.	**Severe** Child was agitated, apathetic, and/or lethargic. He/she required urgent medical attention. There was no need to be a doctor to see that the clinical situation of the child is worrying.
7	Fever	No	Yes, mild rectal or tympanic temperature < 38.5°C, or axillar temperature < 38°C	Yes, moderate rectal or tympanic temperature > 38.5°C, or axillar temperature > 38°C	

17.3 List of Drugs Affecting CCI and CCI

Guidance regarding potential interactions with concomitant medications

E1. Concomitant Medications Relevant to RSV521

A clinical DDI study (REVC004) studied the effect of RV521 on the exposure of an index CYP3A4 substrate, midazolam, and the effects of a CYP3A4 inhibitor, itraconazole, a PGP inhibitor, verapamil and a CYP3A4 inducer, rifampicin on the exposure of RV521. The study has completed. The study suggests that RV521 can CCI the exposure (Cmax and AUC_{0-12}) of CCI by approximately CCI and CCI fold, respectively. The study also demonstrated that the CCI, CCI the exposure (Cmax and AUC_{0-12}) of RV521 by approximately CCI and CCI fold, respectively and the CCI, similarly CCI the exposure (both Cmax and AUC_{0-12}) of RV521 by approximately CCI. Additionally, the CCI the exposure (Cmax and AUC_{0-12}) of RV521 by approximately CCI and CCI fold, respectively.

Therefore, it is anticipated that the exposure of RSV521 may be affected by drugs that CCI or CCI. Table E1 provides a list of CCI. Table E2 provides a list of CCI. Patients receiving CCI or CCI within CCI days before the first dose are excluded from enrolment in the study. If patients require any of these medications during the dosing period of the study then they should be withdrawn from the study.

It is also anticipated that RV521 will affect the exposure of some CCI substrates that have a narrow therapeutic range as RV521 is shown to be a CCI. Table E3 provides a list of CCI substrates. Patients receiving drugs which are known to be CCI substrates within 2 weeks before the first dose of study treatment are excluded from enrolment in the study.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to CCI activity or may be affected by CCI. If required, please refer to full prescribing information for all drugs prior to co-administration with RSV521.

Table E1 CCI which may increase exposure to RV521 and are prohibited in the study

CCI		

Table E2 CCI **which may decrease exporsure to RV521 and are prohibited in the study**

CCI		

Table E3 CCI **substrates that are permitted during the study at the investigator's discretion and with close monitoring**

CCI		

17.4 RSV-related Signs and Symptoms to be Collected

Temperature enter_____
Respiratory Rate enter_____

Coryza	None ☐	Mild ☐	Moderate ☐	Severe☐
Cough	None ☐	Mild ☐	Moderate ☐	Severe☐

Grunting with expiration	None ☐	Present ☐		
Nasal flaring	None ☐	Present ☐		
Retractions	None ☐	Mild ☐	Moderate ☐	Severe☐
Wheezing	None ☐	Mild ☐	Moderate ☐	Severe☐

SpO_2 on room air enter_____

17.5 Dehydration Evaluation – Part of Physical Examination

Dehydration: None ☐ Mild 3-5% ☐ Moderate 6-10% ☐ Severe > 10%☐

Dehydration%	**Mild 3% to 5%**	**Moderate 6% to 10%**	**Severe > 10%**
Mental status	Normal	Listless, irritable	Lethargy, altered mental status
Heart rate	Normal	Increased	Increased
Quality of Pulses	Normal	Normal to decreased	Decreased to thready
Capillary refill	Normal	Prolonged	Prolonged
Blood pressure	Normal	Normal	Normal to decreased
Respirations	Normal	Tachypnea	Tachypnea, deep
Eyes	Normal	Slightly sunken, decreased tears	Sunken, cries without tears
Fontanelle	Normal	Sunken	Sunken
Urine output	Normal to decreased	Decreased	Oliguric or anuric

Source: Vega RM, 2019

Note: This is a guide for the investigator. Just enter category, DO NOT enter each factor.

17.6 ReSVinet Scale for Clinicians

	Item	0 points	1 points	2 points	3 points
1	**Feeding intolerance**	**No**	**Mild** Decreased appetite and/or isolated vomits with cough.	**Partial** Frequent vomits with cough, rejected feed but able to tolerate fluids sufficiently to ensure hydration.	**Total** Oral intolerance or absolute rejection of oral feed, not able to guarantee adequate hydration orally. Required nasogastric and/or intravenous fluids
2	**Medical intervention**	**No**	**Basic** Nasal secretions aspiration, physical examination, trial of nebulized bronchodilators, antipyretics.	**Intermediate** Oxygen therapy required. Complementary exams were needed (chest X-rays, blood gases, hematimetry...). Maintained nebulized therapy with bronchodilators.	**High** Required respiratory support with positive pressure (either non-invasive in CPAP, BiPAP or high-flow O2; or invasive through endotracheal tube).
3	**Respiratory difficulty**	**No**	**Mild** Not in basal situation but does not appear severe. Wheezing only audible with stethoscope, good air entrance. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates mild severity.	**Moderate** Makes some extra respiratory effort (intercostal and/or tracheosternal retraction). Presented expiratory wheezing audible even without stethoscope, and air entrance may be decreased in localized areas. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates moderate severity.	**Severe** Respiratory effort is obvious. Inspiratory and expiratory wheezing and/or clearly decreased air entry. If modified Wood Downes, Wang score or any other respiratory distress score is applied, it indicates high severity.
4	**Respiratory frequency**	**Normal** < 2 m: 40–50 bpm 2–6 m: 35–45 bpm 6-12m: 30–40 bpm 12-24m:25–35 bpm 24-36m: 20–30 bpm	**Mild or occasional tachypnea** Presented episodes of tachypnea, well tolerated, limited in time by self-resolution or response to secretion aspiration or nebulization.	**Prolonged or recurrent tachypnea** Tachypnea persisted or recurred despite secretion aspiration and/or nebulization with bronchodilators.	**Severe alteration** Severe and sustained tachypnea. Very superficial and quick breath rate. Normal/low breath rate with obvious increased respiratory effort and/or mental status affected. Orientative rates of severe tachypnea: < 2 m: > 70 bpm 2–6 m: > 60 bpm 6-12m: >55 bpm 12-24m: >50 bpm 24-36m: >40 bpm
5	**Apnea**	**No**			**Yes** At least one episode of respiratory pause medically documented or strongly suggested through anamnesis.
6	**General Condition**	**Normal**	**Mild** Not in basal situation, child was mildly uncomfortable but does not appear to be in a severe condition, not impress of severity. Parents are not alarmed. Could wait in the waiting room or even stay at home.	**Moderate** Patient looks ill, and will need medical exam and eventually further complementary exams and/or therapy. Parents are concerned. Cannot wait in the waiting room.	**Severe** Agitated, apathetic, lethargic. No need of medical training to realize severity. Parents are very concerned. Immediate medical evaluation and/or intervention were required.
7	**Fever**	**No**	**Yes, mild** Central T < 38.5°C	**Yes, moderate** Central T > 38.5°C	

(m = months)