Statistical Analysis Plan for Interventional Studies

Sponsor Name: ReViral Ltd

Protocol Number: REVC003

Protocol Title: A Phase 2a 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)

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CCI [redacted]

Authors: PPD

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1.0	09-Oct-2020	PPD	Initial Release Version
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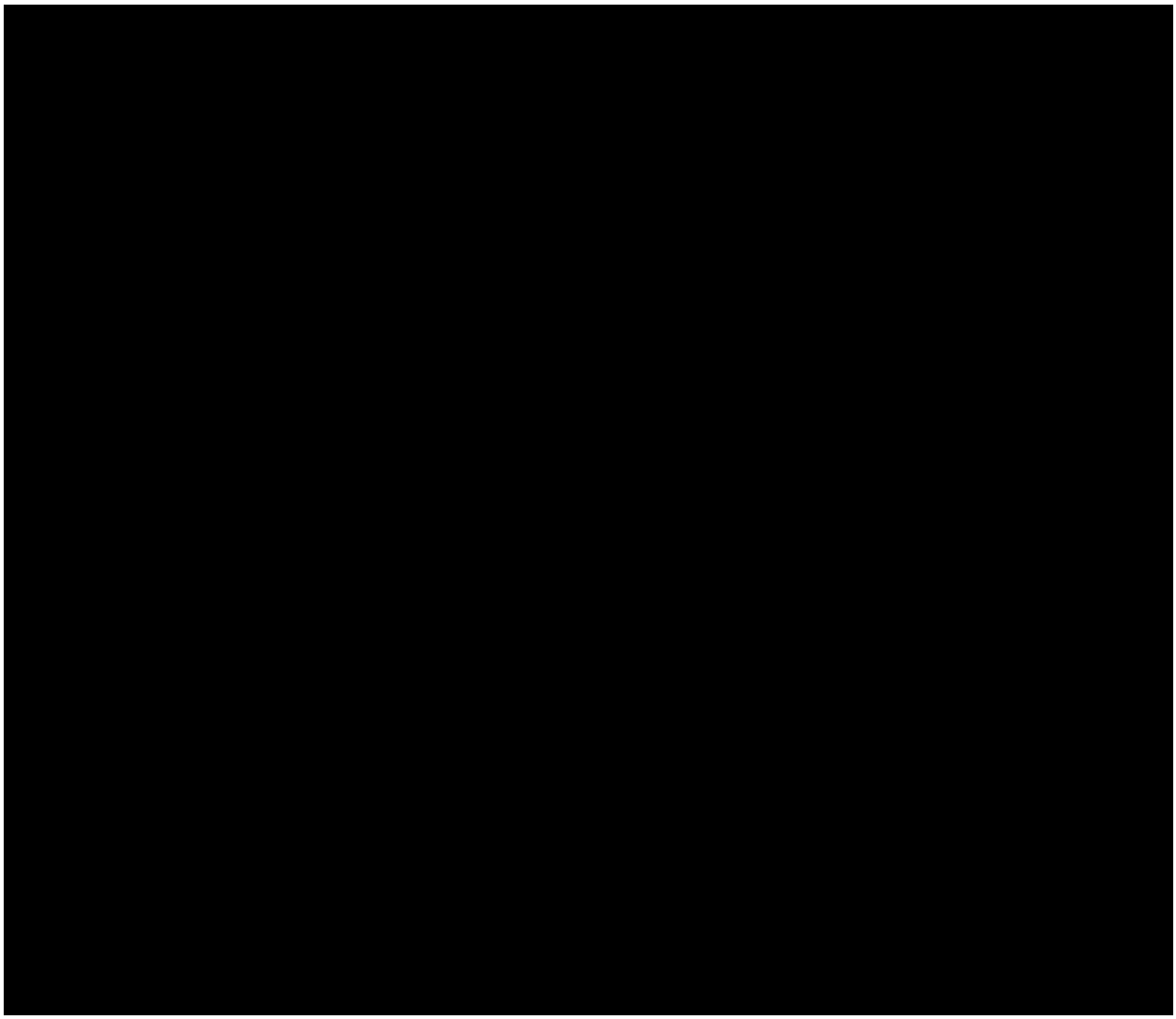

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the 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
BMI	Body Mass index
C_{12}	Trough Concentration at the End of 1st Dosing Interval
C_{ave}	Average Plasma Concentration over Dosing Interval
CBIA	Cell-based Infectivity Assay
CL/F	Apparent total body clearance
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Minimum Observed Plasma Concentration
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events (AEs)
C_{trough}	Plasma Trough Concentration
CV	Coefficient of Variation
DSMC	Data Safety Monitoring Committee
EC_{90}	90% of the effective concentration
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IV	Intravenous
LLoQ	Lower Limit of Quantification
LoD	Limit of Detection

Abbreviation	Description
LRTI	Lower Respiratory Tract Infection
lsmean	Least Square Mean
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent-to-Treat
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RSV	Respiratory Syncytial Virus
RT-qPCR	Reverse Transcriptase Quantitative Polymerase Chain Reaction
SAE	Serious AE
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal Half-life
TEAE	Treatment Emergent AE
t_{max}	Time to Maximum Plasma Concentration
TFL	Tables, Figures and Listings
V/F	Apparent Volume of Distribution of the Drug after Extravascular Administration
WHO	World Health Organisation

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings (TFLs).

2.2. Timings of Analyses

The primary analysis of safety, tolerability, pharmacokinetics (PK) and antiviral effect of RV521 for Parts A, B and C are planned after all subjects from the respective study part complete the final study visit or terminate early from the study. The data will therefore be reported in 3 separate parts.

Interim data summaries will be provided to the independent Data Safety Monitoring Committee (DSMC) according to the DSMC Charter or as requested by the DSMC to allow performance of their duties to monitor the safety of the subjects enrolled in the study.

3. Study Objectives

3.1. Primary Objectives

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).

3.2. Secondary Objectives

- To characterise the PK of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalised with RSV LRTI. Note that in Spain, this was promoted to a primary objective.
- Part B: To evaluate the antiviral effects of RV521 in infants hospitalised with RSV LRTI.
- Part B: To evaluate the effect of RV521 compared to placebo on the clinical course of RSV infection.

3.3. Exploratory Objectives

- CCI [redacted]

[redacted]

3.4. Objectives for Part C

- Primary Objective: To evaluate the effect of RV521, compared to placebo, on the clinical course of RSV LRTI.
- Secondary Objectives:
  - Evaluate the safety of RV521 given as a multiple dose regimen.
  - Effect of RV521, compared to placebo, on nasopharyngeal shedding (viral load) of RSV.
  - CCI [redacted]
  - CCI [redacted]

3.5. Brief Description

The clinical study consists of 3 parts, the third part (Part C) is optional:

- 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, double-blind, placebo-controlled, multicentre, multiple-dose study in infants 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 DSMC.

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× 90% of the effective concentration [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. PK 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.

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

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, i.e., 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 after the completion of Cohort 4. Enrolment in Cohort 5 will continue until 24 evaluable subjects have received RV521 or placebo (2:1) at the dosage and dosing regimen specified for each age group (4 subjects from each of Cohorts 3 and 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.

Based on the results/conclusions of the interim analysis of the safety, PK, and antiviral data following the completion of Part B, there will be an option to enrol up to 120 subjects in Part C if the following conditions are met:

1. A dose has been identified that fulfils the target PK profile.
2. Following review by the DSMC, safety at the selected dose is considered acceptable.
3. Sufficient antiviral effect has been identified to support the probability of an effect on the clinical manifestations of RSV infection.

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

Part C is a double-blind and placebo-controlled study, enrolling 1 cohort (Cohort 6) of approximately 120 subjects (≥ 1 month to ≤ 36 months of age). After a parent/legal guardian provides informed consent, and conditional to satisfactory fulfilment of all inclusion criteria and none of the exclusion criteria (as for Parts A and B), subjects will be randomised 1:1 to receive RV521 or matching placebo. RV521 or placebo will be administered according to the dose and regimen specified for the age group following completion of Part B/ Cohort 5 subjects. Subjects will be followed for safety and tolerability. Clinical findings related to RSV infection will be monitored. The DSMC will evaluate safety data at intervals specified in the DSMC Charter. Nasopharyngeal swabs will be obtained over the course of the study period to evaluate viral load, presence of other respiratory pathogens and CCI [redacted].

Subjects will participate for 29 days, and the visit schedule will include:
Screening (-24 hours to first dose), Dosing (5 days), and Follow-Up 40-48 hours Post-Dose 10 (Visit Day 7) and Study Days 14, and 28. Inpatient duration will be a minimum of 3 days, with duration determined clinically by the PI or other health care provider. Follow-Up days are expected to be on an outpatient basis.

3.6. Subject Selection

3.6.1. Number of Planned Subjects

Approximately 184 subjects (24 subjects in Part A, 40 subjects in Part B, and approximately 120 subjects in Part C) 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 88 to 112 subjects will receive RV521 (12-24 subjects in Part A, 16-28 in Part B, and approximately 60 in Part C), and 68 to 72 subjects will receive placebo (8-12 subjects in Part B and approximately 60 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. The actual number of subjects enrolled in Part C is 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 120 enrolled subjects is attained.

3.6.2. 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
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 (e.g., 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 a minimum of 3 days (administration of 6 doses for both Parts B and C)

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

3.6.3. 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 (e.g., trisomy 21); cardiopulmonary diseases (e.g., haemodynamically significant congenital heart disease); pulmonary disease (e.g., 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. 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

4. Any clinically significant electrocardiogram (ECG) abnormalities

5. Known to be immunocompromised

6. High risk of having developing asthma. Features that indicate a high likelihood of asthma in a young child include:

    a. Symptoms (cough, wheeze, heavy breathing) for > 10 days during upper respiratory infections

    b. > 3 wheezing episodes per year (during the previous 12 months) or severe episodes and/or night wheezing

    c. Between episodes, child has cough, wheeze, or heavy breathing during play or when laughing

    d. Atopy or family history of asthma in a first degree relative

7. 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

8. Has significant oral and/or maxillofacial malformations that would limit the ability to administer IMP

9. History of renal failure including renal anomalies likely to be associated with renal insufficiency (e.g., clinical conditions of renal dysplasia, polycystic renal disease, renal agenesis)

10. Clinical evidence of hepatic decompensation (e.g., 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)

11. History of epilepsy or seizures, including febrile seizures

12. Allergy to test medication or constituents

13. Requires any prohibited medication/therapy as listed in the body of the protocol

    e. Receiving treatment with inhaled, oral, or intravenous (IV) corticosteroids and requires continued corticosteroid therapy

    f. Has taken within 21 days before dosing, any drug that could impact by any mechanism of action on the PK of the investigational product including any CCI [redacted]; or the use of prescription medications, over-the-counter (OTC) medications, herbal remedies or dietary supplements containing CCI [redacted], or the consumption of drugs or other substances CCI [redacted]

    g. Requires the use of Heliox, Leukotriene receptor antagonist (e.g., Montelukast, exogenous surfactant, mucolytics or Hypertonic saline [allowed in the Part A of the study])

14. Has received 1 or more doses of palivizumab at any time before Screening or received treatment with antiviral therapy for RSV (e.g., ribavirin or 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.

15. The subject's parent(s) or legal guardian(s) is a study team member (i.e., 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

16. Currently participating in any investigational study or has participated in an investigational study within 3 months before the Screening Visit

17. Any other reason which in the opinion of the Investigator makes the participant unsuitable for a

clinical trial

3.7. Determination of Sample Size

Because of the exploratory nature of the study, a formal sample size calculation has not been performed. 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 a median time to resolution of symptoms (defined as the interval from day randomisation to the day on which all symptoms of RSV are recorded as absent [severity = 0]) of 15 days with inter-quartile range = 9 days (Petruzella et al, 2010). A total sample size of 120 subjects randomised 1:1 (RV521:placebo) yields a power of 80% to detect a reduction in median time to resolution of symptoms of 30% by Generalised Wilcoxon analysis and assuming a drop-out rate of 15%. Median time to improvement is defined as the interval from day randomisation to the day on which symptoms of RSV present at study entry are recorded as mild or absent (severity =0) and is estimated to be 4 days (IQR = 3 to 7.5 days) (Mansbach et al, 2015).

3.8. Treatment Assignment & Blinding

3.8.1. Treatment Assignment

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 Protocol 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 Protocol Section 8.1.

For Part C Cohort 6, the randomisation list will be designed such that the total of approximately 120 subjects are randomised to receive RV521 or placebo (1:1).

Randomisation in Part C will be stratified by:

1. Duration of symptoms defined as the time first symptom reported by parent until randomisation, < 4 days or ≥ 4 days

2. Severity of illness, defined by the RSV Scoring <9 (mild-moderate) or ≥9 (severe)

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

3.8.2. 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 drug. The randomisation schedule may be shared with other groups outside of the Syneos Health study team (e.g., 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 TFLs 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.

3.9. Administration of Study Medication

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 water or other suspending diluent prior to oral administration on a mg/kg basis.

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, predominantly via syringe, dosing via nasogastric tube is permitted when the Principal Investigator, in their medical opinion deems this appropriate.

Part A:

A single oral dose of RV521 will 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, i.e., 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 the PK and safety data 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 after the completion of Cohort 4. Enrolment in Cohort 5 will continue until 24 evaluable subjects have received RV521 or placebo (2:1) at the dosage and dosing regimen specified for each age group (4 subjects from each of Cohorts 3 and 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 randomised 1:1 to receive RV521 or placebo, according to the dose and regimen specified for their age group following completion of Part B (Cohort 5 subjects).

3.10. Study Procedures and Flowchart

The schedule of planned study assessments for Part A is shown in Table 1, in Table 2 for Part B, and in Table 3 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, e.g., 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. However, all references to PK and nasopharyngeal swab time points pre- and post-Dose 6 will now refer to Dose 3; Dose 5 would be the final dose in the dosing regimen.

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	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	
PK Blood Sample[l]				X	X	X[m]	X		X	
Study Medication Administration[n]			X							
Nasopharyngeal Swab[o]		X				X	X	X	X	
Concomitant Medication Review	X	X	X	X	X	X	X		X	X
AEs Review	X	X	X	X	X	X	X		X	X

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.(Protocol Section 10.1.3.8).

[d] Refer to Protocol 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 Protocol 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); e.g., 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.

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	+4-5h Or +6-8h					0 h	+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															
Inclusion / Exclusion Criteria	X	X														
Demographics[b]	X															
Medical History	X															
Prior Medication Review	X															
Physical Examination[c]	X	X													X	
Hydration Status[d]	X	X				X		X			X*		X*		X	
Body Weight / Length / Head Circumference	X														X	
Vital Signs[e]	X	X	X	X	X	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	+4-5h Or +6-8h					0 h	+4-5 h or +6-8h				Last Dose	+40-48h Post-Dose 10	Day 12
12-Lead ECG[f]	X			X		X		X		X		X*		X*	X	
RSV Clinical Scoring System[g]	X	X				X		X			X*		X*		X	
Record RSV Signs and Symptoms[h]	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*		
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	
Urinalysis	X														X	
Randomisation for Eligible Subjects		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	+4-5h Or +6-8h					0 h	+4-5 h or +6-8h				Last Dose	+40-48h Post-Dose 10	Day 12
PK Blood Sample[k]				X[l]	X[m]				X	X[l]	X[m]				X	
Nasopharyngeal Swab[n]		X			X	X	X	X	X		X*[o]	X*	X*	X*	X	
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Administration[p]			X		X	X	X	X	X		X	X	X	X		

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 +40-48h 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 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 (Protocol 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 Protocol 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 Protocol Appendix 17.1 for the RSV Clinical Scoring System. Note: this assessment is to be done only when subject is hospitalised.

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

[i] Refer to Protocol 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); e.g., 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 two samples will be requested, the other one 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] 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).

[p] 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 DSMC with a time window of **±** 30 minutes.

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

Table 3. Schedule of Assessments for Part C

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	Visit Day 28
Time Relative to Dose	-24 to first dose	-2 to 0 h	0 h	+4-5 h Or +6-8 h					0 h	4-5 h Or +6-8 h				Last Dose	+40-48 h Post-Dose 10	Day 14	Day 28
Written Informed Consent[a]	X																
Inclusion / Exclusion Criteria	X	X															
RSV Rapid Diagnostic Test	X																
Demographics[b]	X																
Medical History	X																
Prior Medication Review	X																
Physical Examination[c]	X	X													X		
Hydration Status[d]	X	X				X		X			X*		X*		X		
Body Weight / Length / Head Circumference	X														X	X	X
Vital Signs[e]	X	X		X	X	X	X	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	Visit Day 28
Time Relative to Dose	-24 to first dose	-2 to 0 h	0 h	+4-5 h Or +6-8 h					0 h	4-5 h Or +6-8 h				Last Dose	+40-48 h Post-Dose 10	Day 14	Day 28
12-Lead ECG[f]	X			X		X		X		X		X*		X*	X		
RSV Clinical Scoring System[g]	X	X				X		X			X*		X*		X	X	X
Record RSV Signs and Symptoms[h]	X	X			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*			
Pulse Oximetry on Room Air		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		
Urinalysis	X														X		
Randomisation for Eligible Subjects		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	Visit Day 28
Time Relative to Dose	-24 to first dose	-2 to 0 h	0 h	+4-5 h Or +6-8 h					0 h	4-5 h Or +6-8 h				Last Dose	+40-48 h Post-Dose 10	Day 14	Day 28
PK Blood Sample[k]									X	X[l]					X		
Nasopharyngeal Swab[m]		X			X	X	X	X	X		X[n]*	X*	X*	X*	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X*	X*	X*	X*	X	X	X
AEs Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Administration[o]			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-p +40-48h 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.

[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 (Protocol 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 Protocol 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 Protocol Appendix 17.1 for the RSV Clinical Scoring System. Note: this assessment is to be done only when subject is hospitalised.

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

[i] Refer to Protocol 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); e.g., 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 two samples will be requested, the other one will not be required (Table 5).

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

[n] 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).

[o] 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 DSMC with a time window of **±** 30 minutes.

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

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 28
A	-2 h to 0 Pre-Dose	12 h Post Dose 1	1 sample collected 24 h post-dose	2 samples: 1 collected at 36 and 1 at 48 h Post Dose 1	NA	NA	NA	NA	NA	NA	NA
B	-2 h to 0 h Pre-Dose	12 h Post Dose 1 (pre-dose 2)	NA	NA	1 sample collected prior to each dose; 2 samples in total[b]	1 sample collected prior to each dose; 2 samples in total[ab]	1 sample collected prior to each dose; 2 samples in total*[b]	1 sample collected prior to each dose; 2 samples in total*[b]	+40-48 h post-Dose 10	NA	NA
C	-2h to 0 pre-dose[b]	12 h Post Dose 1 (pre-dose 2) [b]	NA	NA	1 sample collected prior to each dose; 2 samples in total[b]	1 sample collected prior to each dose; 2 samples in total[ab]	1 sample collected prior to each dose; 2 samples in total*[b]	1 sample collected prior to each dose; 2 samples in total*[b]	+40-48h post Dose 10	1 Sample	1 Sample

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 +40-48h 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 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.
[b] Nasopharyngeal swab sampling window is 60 minutes.
* 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	4-5h, 6-8h, 12h[a],18-24h, 48h	NA	NA	NA	NA	NA	5
B*: Multiple Dose	4-5h or 6-8 h Post-Dose 1, 12h[a] Post-Dose 1 (Pre-Dose 2)	NA	Pre-Dose 6, 4-5h or 6-8h Post-Dose 6.	12h[a] Post-Dose 6 (Pre-Dose 7)	NA	40-48h Post-Dose 10	6
C**: Multiple Dose		NA	Pre-Dose 6 4-5h or 6-8h Post-Dose 6	NA	NA	40-48h Post-Dose 10	3

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 +40-48h 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 4-5h Post Dose 1 or 6-8h Post-Dose 1. The same time point will be taken on Dosing Visit 3 (either 4-5h or 6-8h 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 18-24h 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, either 4-5h or 6-8h 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 18-24h Post Dose 10 will be taken.
[a] The 12-hour PK sampling window is 30 minutes.

4. Endpoints

4.1. Primary Endpoints

Safety and tolerability parameters to be assessed for study Parts A and B will include, but are not limited to:

- AEs, treatment emergent AEs (TEAEs), serious AEs (SAEs), and withdrawals due to TEAEs
- Physical examinations
- Vital sign parameters (i.e., systolic and diastolic blood pressure, temperature, respiratory rate, heart rate, 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

4.2. Secondary Endpoints

Secondary endpoints (primary endpoints in Spain) related to PK for study Parts A and B 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 1st dosing interval (C_{12}) (data permitting)

In addition for Part B:

- Accumulation ratio, percentage fluctuation
- Area under the plasma concentration time curve from time zero to the end of last dosing interval (AUC_{0-tau})
- Average plasma concentration over dosing interval (C_{ave})

- Minimum observed plasma concentration (C_{min})
- Plasma trough concentration (C_{trough})
- Any other relevant parameters

Secondary endpoints related to assessment of antiviral activity and efficacy for study Part B include but are not limited to:

- RSV viral load measured in nasopharyngeal swabs by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR)
- RSV viral load measured in nasopharyngeal swabs by cell-based infectivity assay (CBIA)
- 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

4.3. Exploratory Endpoints

CCI [redacted]

- [redacted]
- [redacted]

4.4. Endpoints for Part C

Endpoints for study Part C include but are not limited to:

Primary Endpoints for Part C

- Time to resolution of symptoms
- Time to improvement of 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 oxygen provided

Secondary Endpoints for Part C

- Safety of RV521 compared to placebo assessed by incidences of AEs, discontinuations due to AEs, SAEs, and clinically significant changes in laboratory tests
- Comparison between RV521 and placebo for changes in viral load over time as for Part B
- CCI [redacted]

- CCI [redacted]

5. Analysis Populations

5.1. Safety Population

The Safety Population will include all subjects who received at least 1 dose 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.

5.2. mITT Population

The Modified Intent-to-Treat (mITT) Population in Part A will include 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.

The mITT Population in Parts B and C will include all subjects who received at least 1 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 meeting. Potential inclusion of subjects who have not completed at least 6 doses of IMP will be decided by the project team during blind data review meeting.

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

5.3. PK Population

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

5.4. Protocol Deviations

Protocol deviations will be identified through a review of deviations 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.

All protocol deviations will be listed, including a classification of major or minor. Major protocol deviations will be summarised overall and by deviation category for the Safety Population.

6. General Aspects for Statistical Analysis

6.1. General Methods

- Unless otherwise specified, summaries for Part A will be presented by cohort, dose level and overall, summaries for Part B will be presented by cohort, treatment, dose level and overall, and summaries for Part C will be presented by treatment and overall.
- Unless otherwise specified, continuous variables will be summarised using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Means and medians will be presented with one more decimal than the observed values. SD values will be presented with 2 more decimals than the observed values.
- Unless otherwise stated, categorical variables will be summarised using number of observations (n), frequency and percentages of subjects.
- Presentations for PK data are described separately in Section 9. Presentations for PD data are described in Section 10.
- All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings.
- All statistical testing will be 2-sided with an alpha level of 0.05, with no adjustment for multiple comparisons.
- For Part B, formal statistical testing will focus on the 24 subjects treated at the doses used in Cohort 5 that were identified in Cohorts 3 and 4. These 24 subjects comprise the whole of Cohort 5, plus the 4 subjects from each of Cohorts 3 and 4 that were randomized with the selected dose/placebo.
- Where there are multiple assessments at a given time point, only the results recorded on the scheduled time point page of the case report form (CRF) will be used for summarisation, unscheduled assessments will be listed only.

6.2. Key Definitions

Baseline will be defined as the last non-missing result before the first dose of IMP. For ECG baseline, only results from the central ECG machine will be considered.

Study day will be defined relative to Dosing Visit 1, which should be Study Day 1. For Part A, study day will be calculated as date of event-date of study medication administration+1 if the event is on or after Dosing Visit 1 and as date of event-date of study medication administration if the event is before Dosing Visit 1. For Parts B and C, study day will be calculated as date of event-date of randomisation+1 if the event is on or after the date of randomisation and as date of event-date of randomisation if the event is before the date of randomisation.

6.3. Missing Data

Data from subjects who withdraw will be included, where possible, in all summaries and analyses.

In order to classify medications documented on the Prior and Concomitant Medications CRF as prior or concomitant, missing and partial medication dates will be handled as in Section 7.5.

Missing time to improvement and time to resolution of RSV-related signs and symptoms will be handled as in Section 8.3. No other imputation of missing efficacy data will be done.

PK concentrations before the first or single dose will be imputed as 0 to reduce the number of PK samples. No other imputation of missing PK data will be done.

Missing PD data will be handled as in Section 10.

In order to assign treatment-emergence, AEs with missing or partial dates will be handled as in Section 12.3.

In order to summarise AEs by relationship and severity, AEs with missing relatedness or severity will be handled as in Section 12.3.

6.4. Visit Windows

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.

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.

6.5. Pooling of Centres

No formal pooling of centres is planned. CCI [redacted]

6.6. Subgroups

For Study Part C, all tables for the primary efficacy endpoints of RSV-related signs and symptoms, RSV Clinical Scoring System score and supplemental oxygen use and all pharmacodynamics tables will be presented by the following subgroups:

- Duration of symptoms prior to randomisation: < 4 days or ≥ 4 days.
- Severity of illness at randomisation: RSV score < 9 (mild-moderate) or ≥ 9 (severe).
- Baseline RSV subtype by RT-qPCR (A or B or Both.)
- Presence or absence of other known respiratory pathogens at baseline.
- Age group (≥ 1 month to < 6 months or ≥ 6 months to ≤ 36 months at screening.)
- Other subgroups may also be presented.

7. Demographic, Other Baseline Characteristics and Medication

No formal statistical testing will be carried out on these data.

7.1. Subject Disposition and Withdrawals

Subject randomisation details will be listed for all subjects allocated to Study Parts B and C. Subject disposition will be listed for all subjects in the database.

For Part A, the number and percentage of subjects treated, completed and withdrawn, together with the reasons for withdrawal, will be summarised for all subjects in the database.

For Parts B and C, the number and percentage of subjects randomised, replaced, treated, completed and withdrawn, together with the reasons for withdrawal, will be summarised for all subjects in the database.

The number and percentage of subjects included, and reasons for exclusion, from each of the analysis populations will be summarised for each study part.

7.2. Demographics

Demographic data will be listed for all subjects.

Demographic data (age, sex, race, ethnicity) will be summarised descriptively. Age at screening (months) will be calculated as (date of screening – date of birth)*12/365.25 and presented to 1 decimal place.

Demographics will be summarised for the Safety, mITT and PK Populations.

7.3. Medical History and Concomitant Diseases

Relevant medical history, including surgical history, will be recorded on the CRF. The study disease (RSV LRTI) will not be entered as a medical history record.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 for prior and concomitant diseases.

Medical history will be summarised by body system, as provided on the CRF, and preferred term (PT), as coded, using summary statistics for categorical data for the Safety Population, and sorted alphabetically by body system and PT.

Medical history data will be listed for all subjects with medical history and presented by record number.

7.4. Other Baseline Characteristics

CCI [redacted] For Parts B and C, the number and percentage of subjects that only have RSV and the number and percentage of subjects who also have other respiratory pathogens will be summarised for the Safety, mITT and PK Populations.

RSV diagnostic test details and CCI [redacted] results from the central laboratory will be listed for all subjects. Subjects for whom central laboratory results did not match the RSV diagnostic test result will be flagged in the RSV diagnostic test data listing.

7.5. Medication

All prior medication taken within 14 days prior to the study and all concomitant medication taken during the study will be documented in the CRF.

Medications will be coded using the World Health Organisation (WHO) Drug dictionary, WHODrug Global B3 Sept 2019. Prior and concomitant medications separately will be summarised by anatomical main group, therapeutic subgroup and preferred name for the Safety Population. Tables will be sorted by descending incidence of anatomical main group, then alphabetical within therapeutic subgroup and preferred name.

In order to classify medications documented on the Prior and Concomitant Medications CRF as prior or concomitant, missing and partial medication dates will be handled as follows:

Missing medication start dates likely to be after the date of first dose of IMP will be imputed as the date of first dose of IMP.

Missing end dates will be imputed as the date of last contact.

Incomplete medication start dates will be imputed using the earliest possible date implied by the portions of the date provided. If only the year is provided, January 1st of that year will be imputed as the start date. If the month and year are provided, the 1st day of the provided month/year will be imputed as the start date.

Incomplete medication end dates will be imputed using the latest possible date implied by the portions of the date provided. If only the year is provided, December 31st of that year will be imputed as the end date. If the month and year are provided, the last day of the provided month/year will be imputed as the end date. If any imputed end date would be after the subject's date of last contact, then the medication end date will be imputed as the date of last contact.

Prior and concomitant medications will be listed together for all subjects will medications with prior and concomitant medications flagged. The data listing will be sorted by start date, end date, Anatomical Main Group, Therapeutic Subgroup, Preferred Name and Verbatim Term.

7.5.1. Prior Medication

Medications will be classified as prior if the medication stop date is before the treatment start date.

7.5.2. Concomitant Medication

Medications will be classified as concomitant if the medication start date is on or after the treatment start date, or if the medication start date is before the treatment start date and the medication stop date is on or after the treatment start date.

8. Clinical Efficacy

All summaries and analyses of clinical efficacy data will be based on observed data in the mITT Population. No imputation of missing data will be done and there will be no adjustments for multiplicity. Data from subjects who withdraw will be included, where possible, in all summaries and analyses.

8.1. RSV Clinical Scoring System Score

The RSV Clinical Scoring System gives a score from 0 to 12.

For each of Parts A, B and C, the RSV Clinical Scoring System score will be summarised at baseline and at each post-baseline time point. Summary statistics will be provided for the observed values and the corresponding changes from baseline for post-dose assessments. Plots of the mean ± SD observed and change from baseline RSV Clinical Scoring System score by time point (baseline and each post-baseline assessment) will be presented. If necessary, lower SD bars will be truncated at 0 for the observed value plot.

For Part B, comparisons will be made between RV521 and placebo using a mixed effects analysis of covariance (ANCOVA) model on the change from baseline in RSV Clinical Scoring System score including a random effect term for subject, fixed effect terms for treatment group, age group (≥ 1 month to < 6 months or ≥ 6 months to ≤ 36 months at screening), visit and visit by treatment group interaction, and baseline RSV Clinical Scoring System score as a covariate. The model will be fitted to the 24 subjects treated at the final doses selected for Cohort 5 (see Section 6.1).

For Part C, comparisons will be made between RV521 and placebo using a mixed effects ANCOVA model on the change from baseline in RSV Clinical Scoring System score including a random effect term for subject, fixed effect terms for treatment group, visit, visit by treatment group interaction, duration of symptoms prior to randomisation and severity of illness at randomisation, and baseline RSV Clinical Scoring System score as a covariate.

For each model, a point estimate and 95% confidence interval will be calculated for the mean difference between RV521 and placebo.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions of a normal distribution in the parametric approach are not satisfied, investigations into influence of outliers or non-parametric methods will be considered.

In addition, for each of Parts A, B and C, the RSV Clinical Scoring System score will be categorised as:

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

The number and percentage of subjects with mild, moderate and severe assessments will be summarised at baseline and at each post-baseline time point.

All tables for Part C, will also be presented by the subgroups defined in Section 6.6.

8.2. Adapted Version of ReSVinet Scale for Parental Use

The Adapted Version of ReSVinet Scale for Parental Use is used in study Parts B and C and gives a score from 0 to 20.

For Parts B and C, the continuous Adapted Version of ReSVinet Scale for Parental Use scores will be summarised and analysed as for the RSV Clinical Scoring System scores.

8.3. RSV-related Signs and Symptoms

RSV-related signs and symptoms (temperature, respiratory rate, coryza, cough, grunting with expiration, nasal flaring, retractions, wheezing and SpO2 on Room air) will be collected on the CRF at each time point identified in the Schedule of Assessments for Part B (Table 2), and Part C (Table 3) in Section 3.10.

For study Parts B and C, assessments of individual RSV-related signs and symptoms will be summarised at each time point. For quantitative variables, observed values and changes from baseline will be summarised. In addition, highest level of severity during the study for each individual RSV-related sign and symptom will be summarised using summary statistics for categorical variables.

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 severity=0) or mild. If there is no improvement, then time to improvement will be censored as the date/time RSV-related signs and symptoms were last recorded. Time to improvement will be summarised (number [%] of subjects analysed, mean, median, SD, minimum, maximum) for Parts B and C. 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 Parts B and C by n, mean, median, SD, minimum, maximum and 95% confidence intervals for the mean. For Part C only, time to improvement of symptoms and overall time to improvement, will be compared between RV521 and Placebo using a Generalised Wilcoxon analysis, which is a weighted log-rank test, weighted by the number of subjects at risk immediately prior to the event, and will include duration of symptoms prior to randomisation as a covariate. Also for Part C only, Kaplan-Meier plots for time to improvement of symptoms and overall time to improvement will be presented by treatment.

Time to resolution will be calculated for RSV-related signs and symptoms that are present at study start and will be defined as the time from randomisation until no longer present (absent or severity=0). If there is no resolution, then time to resolution will be censored as the date/time RSV-related signs and symptoms were last recorded. The overall time to resolution will be defined as the time from randomisation to the time that all RSV-related signs and symptoms are no longer present (absent or severity=0). The time to resolution and the overall time to resolution will be summarised and analysed as for time to improvement.

Times to improvement or resolution will be presented in days to 1 decimal place.

All tables for Part C, will also be presented by the subgroups defined in Section 6.6.

8.4. Supplemental Oxygen Use

The number and percentage of subjects with supplemental oxygen use will be presented overall, at baseline and at each post-baseline time point. Reason for use of supplemental oxygen use will also be summarised.

Duration of use and overall maximum flow rate of oxygen will be summarised using summary statistics for continuous data. Duration of supplemental oxygen use will be calculated in hours from the start time of first use in the study to the end time of the last use in the study, i.e. ignoring any interruptions, and presented to 1 decimal place.

All tables for Part C, will also be presented by the subgroups defined in Section 6.6.

8.5. Duration of Hospitalisation

Duration of hospitalisation will be calculated in days to 1 decimal place from time of informed consent to time of discharge, or time of last AE review if not discharged, and summarised using summary statistics for continuous data. CCI

8.6. Hydration Status

For each of Parts A, B and C, dehydration will be recorded as:

- None.
- Mild 3-5%.
- Moderate 6-10%.
- Severe >10-15%.

The number and percentage of subjects with none, mild, moderate and severe dehydration will be summarised at baseline and at each post-baseline time point.

9. Analysis Of Pharmacokinetics (PK)

PK parameters will be generated using Phoenix WinNonlin version 8 (Pharsight Corporation, Mountain View, California, USA).

9.1. PK Sampling Schedule

Blood samples for measurement of plasma concentrations of RV521 will be drawn at time points specified in the Schedule of Assessments in Section 3.10. 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. 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 plasma concentrations of RV521. 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 plasma 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.

9.2. Plasma PK Endpoint

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

Data regarding exposure after accumulation will be compared to parameters observed in adult subjects (C_{max}, AUC_{0-tau}, C_{12} [data permitting]).

9.3. Presentation of Concentration Data

9.3.1. Handling of Missing Data

PK concentrations before the first or single dose will be imputed as 0 to reduce the number of PK samples.

The profiles for all subjects including those with incomplete sampling profiles will be used to inform the population PK model. The results of the model will be used to simulate profiles and estimate non-compartmental parameters from the simulations. This is not considered to be an imputation of missing data and will be performed for all subjects who receive active treatment irrespective of the number of available PK samples.

9.3.2. Listing and Presentation of Individual PK Data

All plasma RV521 concentration data will be listed for the PK Population. No imputed data will be included in the data listings. Individual subject linear plasma RV521 concentration-time plots will be presented on a linear scale and on a log-linear scale, using actual times relative to dose for Part A and using nominal times relative to dose for Parts B and C.

For the calculation of summary statistics, plasma RV521 concentrations that are below the limit of quantification (BLQ) will be treated as 0.

Plasma RV521 concentration data will be summarised at each nominal time point (n, number of values below BLQ [nBLQ], mean, SD, coefficient of variation (CV), minimum, median, maximum, geometric mean, and geometric CV) for the PK Population. Reporting precision for summaries of plasma RV521 concentration data will be the same as that for the PK Parameters in Section 9.4.1.

Mean ± SD plasma RV521 concentration-time profiles will be presented on a linear scale using nominal times for the PK Population, lower SD bars will be truncated at 0.

Mean + SD plasma RV521 concentration-time profiles will be presented on a log-linear scale using nominal times for the PK Population, plasma RV521 concentrations that are BLQ will be treated as the limit of quantification value.

9.4. PK Parameters Derivation

The PK parameters will be derived by non-compartmental method from estimated concentration and available observed concentration. Considering the sparse sampling the individual PK concentrations profiles will be estimated using the population PK model and post-hoc Bayesian method.

The PK parameters in Table 6 will be derived for RV521.

Table 6. PK Parameter Determination

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration.	Observed from the PK profile
T_{max}	Time to reach C_{max}. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.	Observed from the PK profile
AUC_{0-t}	Area under the plasma concentration-time curve, from time 0 to the last measurable concentration.	Linear trapezoidal method
AUC_{0-12}	Area under the plasma concentration-time curve, from time 0 to the 12-hour time point (using the scheduled 12-hour sampling time). AUC_{0-12} will be interpolated/ extrapolated if the 12-hour concentration is not collected at the scheduled time, missing or not reportable, as appropriate.	Linear trapezoidal method

Parameter	Definition	Method of Determination
$AUC_{0-\infty}$	Area under the concentration-time curve, from time 0 extrapolated to infinity.	$AUC_{0-t} + C_{last}/K_{el}$, where C_{last} is the concentration at the last measurable time point.
K_{el}	Apparent first-order terminal elimination rate constant.	Estimated by linear regression of the terminal elimination phase of the log-linear drug concentration-time curve
$t_{1/2}$	Apparent first-order terminal elimination half-life.	$ln(2)/K_{el}$
CL/F	Apparent total body clearance.	Estimated as $Dose/AUC_{0-\infty}$
V/F	Apparent volume of distribution.	Estimated as $Dose/(K_{el} \times AUC_{0-\infty})$
C_{12}	Trough concentration at the end of 1st dosing interval	Observed from the PK profile

For Parts B and C, the PK parameters in Table 7 also be derived.

Table 7. PK Parameter Determination – Additional Parameters for Parts B and C

Parameter	Definition	Method of Determination
% Fluctuation	Percentage of fluctuation.	Computed as $100*(C_{max}-C_{min})/C_{ave}$, where C_{min} and C_{max} measured over dosing interval.
T_{max}	Time to reach C_{max}. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.	Observed from the PK profile
AUC_{0-tau}	Area under the plasma concentration-time curve, from time 0 to the end of last dosing interval.	Linear trapezoidal method
C_{ave}	Average plasma concentration over dosing interval.	Estimated as AUC_{0-tau} /tau
C_{trough}	Plasma trough concentration	Observed from the PK profile

9.4.1. PK Parameters Summarisation

Individual subject PK parameters will be listed for the PK Population.

PK parameters will be summarised using descriptive statistics as detailed in Table 8 for the PK Population.

Table 8. PK Parameters – Summary Statistics

Variable	Summarised with:
AUC, C_{max}, C_{ave}, C_{min}, C_{trough}, C_{12}	n, arithmetic mean, SD, CV (%) calculated as 100%*SD/mean, minimum, first quartile (Q1), median, third quartile (Q3), maximum, geometric mean, and geometric CV, calculated as Geometric CV (%) = $100\% * \sqrt{e^{z^2} - 1}$, where z^2 is the variance of $\ln(x_i)$
CL/F, V/F, accumulation ratio, percentage fluctuation	n, arithmetic mean, SD, CV, minimum, Q1, median, Q3, maximum
$T_{1/2}$	n, arithmetic mean, SD, CV, minimum, median, maximum
T_{max}	n, minimum, median, and maximum

The conventions to be used for the presentation of the descriptive statistics of PK parameters and concentrations are detailed in Table 9.

Table 9. PK Parameters – Reporting Precision

Statistics	Degree of Precision
Minimum, Q1, Median, Q3, Maximum	3 significant digits
Mean (arithmetic and geometric)	3 significant digits
SD	3 significant digits
CV and Geometric CV	1 decimal place

9.5. Planned Statistical Models for PK Parameters and Concentrations

None planned.

9.6. Interim Analyses

Interim PK analyses will be performed during Part A and Part B to verify if the previously developed PK model of RV521 adequately predicted the exposure in subjects ≥ 6 months to ≤ 24 months of age and subjects ≥ 1 month to < 6 months of age and report the observed exposure in the infants. The results of these PK analyses, in addition to the safety data, will guide further dosing decision by the DSMC. The PK reports to be generated are provided in the DSMC Charter.

9.7. Deviation from Analyses Planned in Protocol

Currently there are no changes from the analysis planned in the protocol.

10. Analysis Of Pharmacodynamics (PD)

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 3) in Section 3.10. The actual date and time (24-hour clock time) of each sampling will be recorded. 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. All summaries and analyses of PD data will be based on observed data in the mITT Population. Data from subjects who withdraw will be included, where possible, in all summaries and analyses.

All tables for Part C, will also be presented by the subgroups defined in Section 6.6.

10.1. Primary PD Endpoint and Analysis

Separate assays will be used to detect viral load of RSV A separate from RSV B by RT-qPCR. The primary analysis will report the viral load which has been quantified from either subtype, or in the case of co-infection, from the combined activity of both subtypes (total RSV viral load by RT-qPCR). The CBIA detects both RSV A and RSV B simultaneously.

If any RT-qPCR viral load result is less than the limit of detection (LoD) then a value of ½ the LoD will be used in the calculation of total RSV viral load by RT-qPCR. If any RT-qPCR viral load result falls between the LoD and the lower limit of quantification (LLoQ) then a value midway between the LoD and the LLoQ will be used in the calculation of total RSV viral load by RT-qPCR. Using these imputations, the value from each subtype will be added together at each time point to calculate total RSV viral load by RT-qPCR. This method ensures that the data collected from all subjects are consistent and not weighted to those who have both subtypes present. Total RSV viral load by RT-qPCR is calculated before any log transformations are applied.

If any CBIA viral load result is less than the LoD then a value of ½ the LoD will be used for analysis. For each assay, Table 10 shows the LoD values, LLoQ values, reported results and replacement values used for calculations:

Table 10. LoD and LLoQ Replacement Values

Assay	LoD	LLoQ	Reported Result (log10)	Replacement Value (log10)
RT-qPCR RSV A	2.02	2.23	<2.23	Replacement value for <LLoQ, log10(midway between unlogged LLoQ and LoD) = 2.14
RT-qPCR RSV A	2.02	2.23	Negative	Replacement value for <LoD, log10(½ of unlogged LoD) = 1.72
RT-qPCR RSV B	2.33	2.60	<2.60	Replacement value for <LLoQ, log10(midway between unlogged LLoQ and LoD) = 2.49
RT-qPCR RSV B	2.33	2.60	Negative	Replacement value for <LoD, log10(½ of unlogged LoD) = 2.03
CBIA	0.7	N/A	<0.70	Replacement value for <LoD, log10(½ of unlogged LoD) = 0.40

For all study Parts, $\log_{10}$ total RSV viral load measured in nasopharyngeal swabs by RT-qPCR in viral particles per mL, and $\log_{10}$ RSV viral load measured in nasopharyngeal swabs by CBIA in 50% tissue culture infective dose per mL, will be listed to 2 decimal places and summarised by nominal time point (n, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV), including changes from baseline for post-dose measurements, for the mITT Population. All summary statistics will be presented to 2 decimal places, except CV and geometric CV, which will be presented to 1 decimal place.

Plots of the mean +/- SD observed and change from baseline values by nominal time point (baseline and each post-baseline measurement) will be presented.

For Parts B and C, log_{10} total RSV viral load by RT-qPCR and log_{10} RSV viral load by CBIA will also be summarised by nominal time point (n, mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV) and presence or absence of other known respiratory pathogens at baseline for the mITT Population. All summary statistics for viral load will be presented to 2 decimal places, except CV and geometric CV, which will be presented to 1 decimal place.

10.2. Secondary PD Endpoint(s) and Analyses

Secondary PD endpoints will be analysed for Study Parts B and C only. All secondary PD endpoints will be listed to 2 decimal places for the mITT Population. All summary statistics will be presented to 2 decimal places, except CV and geometric CV, which will be presented to 1 decimal place.

10.2.1. Area Under the RSV Viral Load Curve

The DAVG statistic will be used to summarise the change in RSV viral load from baseline over a time period, standardised to a unit of time (sometimes called time weighted average change in RSV viral load), both for total RSV viral load by RT-qPCR and for RSV viral load by CBIA.

The statistic is calculated as: $\text{DAVG} = \frac{\sum_{ii=aa}^{bb} 0.5\,(YY_{ii}+YY_{ii+1})\,(tt_{ii+1}-tt_{ii})}{tt_{bb}-tt_{aa}}$

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.

If subjects have missing viral load data post baseline, then the data that are available will be used to generate the area under the curve (AUC) and will be divided through by the corresponding time period to obtain the DAVG value. Any subjects with less than 1 viral load value post baseline will be excluded from the DAVG calculation and hence from the analysis.

If baseline viral load are missing, an imputation method will be used under the assumption that the data are missing at random. The imputed value will be determined from an ANCOVA model with baseline viral load used as the dependent factor and duration of symptoms prior to randomisation, severity of illness at randomisation and age group (≥ 1 month to < 6 months or ≥ 6 months to ≤ 36 months at screening) as independent factors. The predicted value for the subject with the missing baseline value will be used as the imputed value.

DAVG for total RSV viral load by RT-qPCR and for RSV viral load by CBIA will be summarised (n, arithmetic mean, SD, CV, minimum, Q1, median, Q3, maximum, geometric mean, and geometric CV) by presence or absence of other known respiratory pathogens at baseline and overall for the mITT Population.

For Part B, comparisons will be made between RV521 and placebo using a mixed effects ANCOVA model on the DAVG including a random effect term for subject, fixed effect terms for treatment group, age group (≥ 1 month to < 6 months or ≥ 6 months to ≤ 36 months at screening) and presence or absence of other known respiratory pathogens at baseline, and baseline RSV viral load as a covariate. The model will be fitted to the 24 subjects treated at the final doses selected for Cohort 5 (see Section 6.1).

Furthermore, the above analysis will be repeated but also including a treatment group by presence or absence of the other known respiratory pathogens at baseline interaction, in order to investigate the

treatment effect given the presence or absence of the pathogens.

For Part C, comparisons will be made between RV521 and placebo using a mixed effects ANCOVA model on the DAVG including a random effect term for subject, fixed effect terms for treatment group, presence or absence of other known respiratory pathogens at baseline, duration of symptoms prior to randomisation and severity of illness at randomisation, and baseline RSV viral load as a covariate.

For each model, a point estimate and 95% confidence interval will be calculated for the mean difference between RV521 and placebo. Estimates will also be provided separately by presence or absence of other known respiratory pathogens at baseline.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions of a normal distribution in the parametric approach are not satisfied, investigations into influence of outliers or non-parametric methods will be considered.

10.2.2. Percentage Change From Baseline in RSV Viral Load

Change in $\log_{10}$ viral load from baseline will be calculated to 60 hours and 156 hours after first dose, both for total RSV viral load by RT-qPCR and for RSV viral load by CBIA. No imputation of missing data is planned, but prior to unblinding a check will be made to determine the amount of missing data at 60 and 156 hours and whether an imputation method is warranted.

For Part B, comparisons will be made between RV521 and placebo using a mixed effects ANCOVA model on the change from baseline including a random effect term for subject, fixed effect terms for treatment group, age group (≥ 1 month to < 6 months or ≥ 6 months to ≤ 36 months at screening) andpresence or absence of other known respiratory pathogens at baseline, and baseline RSV viral load as a covariate. The model will be fitted to the 24 subjects treated at the final doses selected for Cohort 5 (see Section 6.1).

Furthermore, the above analysis will be repeated but also including a treatment group by presence or absence of the other known respiratory pathogens at baseline interaction, in order to investigate the treatment effect given the presence or absence of the pathogens.

For Part C, comparisons will be made between RV521 and placebo using a mixed effects ANCOVA model on the change from baseline including a random effect term for subject, fixed effect terms for treatment group, presence or absence of other known respiratory pathogens at baseline, duration of symptoms prior to randomisation and severity of illness at randomisation, and baseline RSV viral load as a covariate.

For both Parts B and C the change from baseline least square mean (lsmean) estimates will be presented for $\log_{10}$ viral load, along with the difference in lsmeans between RV521 and placebo and 95% confidence intervals. In addition the lsmean change from baseline will be back transformed and presented as a percentage change from baseline of the original viral load. Estimates will also be provided separately by presence or absence of other known respiratory pathogens at baseline.

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions of a normal distribution in the parametric approach are not satisfied, investigations into influence of outliers or non-parametric methods will be considered.

10.2.3. CCI

[redacted]

11. CCI

11.1.

11.2. CCI

12. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed on the basis of AE reports, clinical laboratory data, ECG parameters, physical examinations, and vital signs.

12.1. Extent of Exposure

For Study Part A, the number and percentage of subjects with the planned dose administered and the number and percentage of subjects with the planned dose not administered will be summarised for all analysis populations. For Study Parts B and C for all analysis populations, duration of exposure to IMP in days will be summarised as a continuous variable, total number of doses administered will be summarised as a categorical variable, and the numbers and percentages of subjects with all planned doses administered and at least one planned dose not administered will be summarised. For the subjects with at least one planned dose not administered, the number of doses where the planned dose was not administered will be summarised as a categorical variable. Duration of exposure will be calculated from first and last dose times and presented to 1 decimal place. No account will be taken of gaps in medication. All collected IMP administration details and calculated extent of exposure variables, including total volume administered in mL, will be listed for the Safety Population.

12.2. Treatment Compliance

Number of doses where planned dose not administered and number of doses missed will be presented in a data listing for the Safety Population to assess treatment compliance.

12.3. Adverse Events

The Investigator will document all AEs that occur during the study from the time the ICF is signed until the last follow up Visit on the appropriate page of the CRF. Each separate AE episode will be recorded. For example, if an AE resolves completely or resolves to baseline and then recurs or worsens again, this will be recorded as a separate AE. For AEs to be considered intermittent, the events must be of similar nature and severity.

Severity of AEs will be assessed by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for AEs (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.

For purposes of this study the severity will be graded as follows:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3>: Severe

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.

AEs will be coded according to the MedDRA dictionary Version 22.1. Summary tables of AEs will be based on TEAEs, defined as events starting, or worsening, after the first dose of IMP. Treatment-related TEAEs will be defined as TEAEs with causality assessed as possibly, probably, or definitively related to IMP.

In order to assign treatment-emergence, AEs with missing or partial dates are considered treatment-emergent unless there is clear indication that the event occurred before the first dose of IMP. In general, only TEAEs will be included in the summary tables, but all AEs will be included in the data listings.

At each level of summarisation, summaries will include the number and percentage of subjects. For summaries by MedDRA System Organ Class (SOC) and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level. For summaries by SOC, PT, and severity, a subject will be counted once at each severity level for which the event occurred at the SOC level and at each severity level for which the event occurred for each unique PT within that SOC level. Therefore, subjects may contribute to multiple severity levels within a PT or SOC. For summaries by SOC, PT, and maximum severity, a subject will be counted once at the highest severity level for which the event occurred at the SOC level and the highest severity level for each unique PT within that SOC level. Therefore, subjects may only contribute once to each PT and once to each SOC level. AEs with missing severity will be counted as severe. Summaries by maximum relationship will be handled similarly to the summaries by maximum severity. AEs with missing relatedness will be counted as definitely related.

Summaries presenting frequency of AEs by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT.

The following tables will be produced:

- An overall summary of the number and percentage of subjects reporting TEAEs, serious TEAEs, treatment-related TEAEs, TEAEs leading to permanent discontinuation of IMP and TEAEs leading to death.
- TEAEs overall and by SOC and PT.
- TEAEs overall and by SOC, PT and severity.
- TEAEs overall and by SOC, PT and maximum severity.
- TEAEs overall and by SOC, PT and maximum relationship to IMP.
- Treatment-related TEAEs overall and by SOC and PT.
- Serious TEAEs, overall and by SOC and PT.
- TEAEs leading to permanent discontinuation of IMP, overall and by SOC and PT.

12.4. Laboratory Evaluations

Laboratory results will be presented for haematology, chemistry and urinalysis.

All laboratory results will be converted to Standard International units. Results below or above the normal range will be indicated in the listings.

In the presence of re-tests, original results will be used in the summary tables, however all re-test results will be included in the listings.

For each of Parts A, B and C, continuous laboratory results will be summarised at baseline and at each scheduled post-baseline time point. Summary statistics will be provided for the observed values at each time point, and the corresponding change from baseline. Categorical laboratory results for urinalysis will be summarised at baseline and at each scheduled post-baseline time point. The number and percentage of subjects with laboratory measurements outside of the normal reference range will also be summarised at baseline and at each scheduled post-baseline time point.

Laboratory results will be graded according to NCI CTCAE v5.0, for applicable parameters (haemoglobin, white blood cells, platelets, creatinine, AST, ALT, alkaline phosphatase, lactate dehydrogenase, total bilirubin). The severity will be graded as follows:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening

For each applicable parameter, the number and percentage of subjects experiencing each abnormality at any time after first dose will be summarised by severity grade and by maximum severity grade.

Shift tables of laboratory results from baseline to maximum post-dose severity grade, including unscheduled visits, will be presented.

12.5. Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, temperature and pulse oximetry. Temperatures captured in ^{o}F will be converted to ^{o}C using the conversion:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

For each of Parts A, B and C, vital signs will be summarised at baseline and at each post-baseline time point. Summary statistics will be provided for the observed values at each time point, and the corresponding change from baseline. In addition, the investigator's interpretation of the vital signs are also captured. These data will be summarised at baseline and at each post-baseline time point.

Height, weight, body mass index (BMI) and head circumference will also be collected. The following conversions will be used:

Height or circumference (in cm) = height or circumference (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

Following conversion, the above vital signs will be presented to 1 decimal place.

For Parts B and C, height, weight, BMI and head circumference will be summarised at baseline and at each post-baseline time point. Summary statistics will be provided for the observed values at each time point, and the corresponding change from baseline.

12.6. ECG

ECG parameters include ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval.

For each of Parts A, B and C, ECG parameters will be summarised at baseline and at each post-baseline time point. Summary statistics will be provided for the observed values at each time point, and the corresponding change from baseline.

In addition, the investigator's interpretation of the ECGs are also captured. These data will be summarised at baseline and at each post-baseline time point.

Only results from the central ECG machine will be used in the summary tables.

12.7. Physical Examination

Physical examination data will be summarised for each body system at baseline and at each post-baseline time point.

13. Interim Analyses

No formal interim statistical analyses are planned. Interim data summaries and PK analyses will be provided to the DSMC according to the DSMC Charter as per Sections 2.2 and 9.6.

14. Changes from Analysis Planned in Protocol

CCI [redacted]

Clarifications were added to the determination of sample size section.

The definition of the Safety Population was simplified for clarity.

The Efficacy and PD Populations have been replaced by the mITT Population.

The PK Population has been expanded to include all subjects from Cohort 6 who receive IMP and have at least 1 post-dose PK concentration measurement.

The PD variables of $AUC_{(0\text{-}60 \text{ hours post-dose 1})}$ and $AUC_{(0\text{-}156 \text{ hours post-dose 1})}$ have been replaced with an analysis based on DAVG.

15. Changes from Version 1.0 of the SAP

The following updates from Version 1.0 of the SAP, dated 09-Oct-2020 have been made:

- Update to definition of MITT population for Parts B and C to take into account the possibility that we may have subjects who do not ingest the administered doses but who do not withdraw from the study. The following has been added to the definition of the MITT population: 'Inclusion of subjects who have not completed at least 6 doses of IMP will be agreed by the project team during blind data review.'

- For Part B, it is clarified that formal statistical analyses will focus on the 24 subjects treated at the final doses selected for Cohort 5.

- To allow for a different treatment effect to be estimated at each visit, for the RSV Clinical Scoring System and the Adapted Version of ReSVinet Scale for Parental Use, the mixed model analyses will also include fixed effect terms for visit and visit by treatment group interaction. Furthermore, for Part B, as the analyses will focus on the 24 subjects treated at the final doses selected for Cohort 5, dose is no longer required to be fitted to the model as a fixed effect as this is now synonymous with age group.

- For the formal statistical analyses of the PD data for Part B, as the analyses will focus on the 24 subjects treated at the final doses selected for Cohort 5, dose is no longer required to be fitted to the model as a fixed effect as this is now synonymous with age group. In addition, analyses will be repeated with the addition of an interaction term to the model for treatment group by presence or absence of other known respiratory pathogens. This will enable the treatment effect given the presence or absence of the pathogens to be investigated.

16. Reference List

Mansbach JM, Clark S, Piedra PA, et al. Hospital course and discharge criteria for children hospitalised with bronchiolitis. *J Hosp Med*. 2015;10(4):205-11.

Petruzella FD, Gorelick MH. Duration of illness in infants with bronchiolitis evaluated in the emergency department. *Pediatrics*. 2010;126(2):285-290.

17. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS Release 9.4 (SAS Institute Inc., Cary, NC, USA) or higher. Computer-generated table, listing and figure output will adhere to the following specifications.

PK parameters will be generated using Phoenix WinNonlin version 8 (Pharsight Corporation, Mountain View, California, USA).

17.1. General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

17.2. Table, Listing, and Figure Format

17.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8, which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no colour), unless otherwise specified.
- Specialised text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

17.2.2. Headers

- All output should have the following header at the top left of each page:

- ReViral Ltd Protocol REVC003
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

17.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centred. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

17.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables will be Placebo first in the case of placebo controlled studies, followed by a total column (if applicable).

17.2.5. Body of the Data Display

17.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and

- Numbers containing fractional portions are decimal aligned.

17.2.5.2. *Table Conventions*

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and SDs are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by anatomical main group), and AEs (by PT) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

17.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

17.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

17.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

18. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health standard operating procedure (SOP) Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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	CCI		

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CCI [redacted]	[redacted]	[redacted]
[redacted]		[redacted]
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CCI [redacted]	[redacted]	[redacted]
[redacted]		[redacted]
CCI [redacted]		[redacted]
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Not applicable.