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(54) Title: PEDIATRIC DOSING REGIMENS COMPRISING A FUSION INHIBITOR FOR THE TREATMENT OF RSV

(57) Abstract: The invention relates to dosing regimens for the treatment of RSV infection comprising administering to a pediatric subject in need thereof a daily dose of a sisunatovir as a single agent or in combination with other RSV therapies.

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PEDIATRIC DOSING REGIMENS COMPRISING A FUSION INHIBITOR FOR THE TREATMENT OF RSV

Background of the Invention

Respiratory Syncytial Virus (RSV) is a negative-sense, single-stranded RNA virus of the Pneumoviridae family. RSV is readily transmitted by secretions from an infected person via surfaces or hand-to-hand transfer. Following successful inoculation, the incubation period is between four and six days during which time the virus spreads from the nasopharynx to the lower respiratory tract by fusion of infected with uninfected cells and by sloughing of the necrotic epithelium. In infants, coupled with increased mucus secretion and oedema, this can lead to mucus plugging causing hyper-inflation and collapse of distal lung tissue indicative of bronchiolitis. Hypoxia is common and the ability to feed is often impaired because of respiratory distress. In RSV pneumonia, inflammatory infiltration of the airways consists of mononuclear cells and is more generalized, with involvement of the bronchioles, bronchi and alveoli. The duration and degree of viral shedding has been found to correlate with the clinical signs and severity of disease.

RSV is the leading cause of serious respiratory tract infections in infants and young children throughout the world. The highest morbidity and mortality occur in those born prematurely and for those with chronic lung or heart disease, although many infants hospitalized for RSV infection are otherwise healthy. Severe RSV infection in infancy can lead to several years of recurrent wheezing and is linked to the later development of asthma.

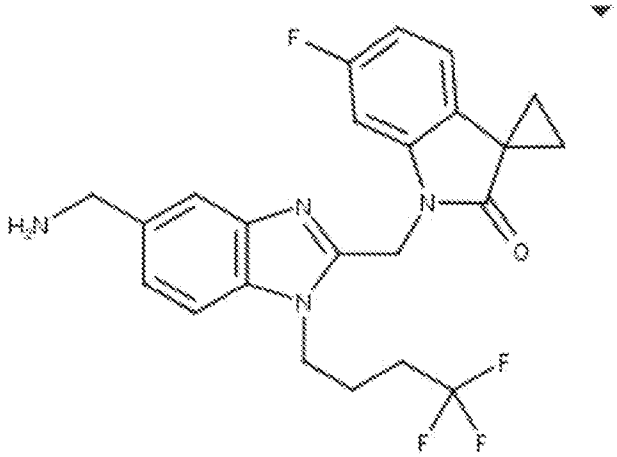
RSV is also a major cause of morbidity and mortality in the elderly and in immunocompromised children and adults as well as those with chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).

Current anti-RSV treatment involves the use of ribavirin or a monoclonal antibody such as palivizumab or nirsevimab. Such use of monoclonal antibodies is usually as a prophylactic, rather than therapeutic, treatment of RSV. Although these antibodies are often effective, their use is restricted to preterm infants and infants at high risk. Indeed, its limited utility means that it is unavailable for many people in need of anti-RSV treatment. There is therefore an urgent need for effective alternatives to existing anti-RSV treatment.

Small molecules have also been proposed as inhibitors of RSV. These include benzimidazoles and benzodiazepines. For instance, benzimidazole inhibitors of RSV are disclosed in WO 02/062290 and WO 03/053344 (Squibb Bristol Myers Co); WO 2010/103306 (Astrazeneca UK Ltd); and WO 2013/068769, WO 2016/055780, WO 2019/016566 and WO 2019/122928 (ReViral Limited). The discovery and initial development of RSV604, a

benzodiazepine compound having sub-micromolar anti-RSV activity, is described in Antimicrobial Agents and Chemotherapy, Sept. 2007, 3346-3353 (Chapman et al). Benzodiazepine inhibitors of RSV are also disclosed in publications including WO 2004/026843 and WO 2005/089770 (Arrow Therapeutics Limited); WO 2016/166546 and WO 2018/033714 (Durham University); WO 2017/015449, WO 2018/129287 and WO 2018/226801 (Enanta Pharmaceuticals, Inc.); and WO 2021/079121, WO 2021/084280, WO 2021/032992, WO 2022/008911 and WO 2022/008912 (ReViral Limited).

1'-{[5-(Aminomethyl)-1-(4,4,4-trifluorobutyl)-1H-1,3-benzodiazol-2-yl]methyl}- 6'-fluoro-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2'-one, also known as sisunatovir, is a respiratory syncytial virus fusion inhibitor currently in phase 2 clinical trials for the treatment of RSV infections and has the following structure:



Sisunatovir and preparation thereof is described in international publication WO 2016/055780. Clinical studies in adults have investigated the pharmacokinetics of sisunatovir (DeVincenzo et al., Antimicrobial Agents and Chemotherapy Feb. 2020 Vol. 64 issue 2). The contents of each of the foregoing documents are incorporated herein by reference in their entirety.

There is however a need for appropriate pediatric dosing regimens of sisunatovir and pharmaceutically acceptable salts thereof, as a single agent or in combination therapies for treating RSV infection, to improve benefit and convenience to pediatric patients while minimizing adverse events and risks to them.

Based on what is currently known, sisunatovir hydrochloride salt (HCl) adult dosing is expected to be 200 mg twice daily (DeVincenzo et al). Based on allometric scaling, pediatric doses with comparable exposure to adults was predicted to be approximately 2 mg/kg for pediatric patients aged 1 month to < 6 months and 2.5 mg/kg for pediatric patients aged 6 months to 36 months. However, it was unexpectedly found these doses resulted in unacceptably low exposures compared to adults and that the dose to pediatric patients aged 1 to 60 months should be much higher to achieve comparable exposure to adult patients.

Summary of the Invention

The present invention provides, in part, dosing regimens for administering sisunatovir, or a pharmaceutically acceptable salt thereof, to a subject as a single agent, and in combination therapies, for treating RSV infection in pediatric populations. This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used in isolation as an aid in determining the scope of the claimed subject matter.

According to an embodiment of the invention, there is provided a method for treating RSV infection comprising administering to a 1- to 60-month-old subject in need thereof a dose of from about 4.0 mg/kg to about 8.0 mg/kg of sisunatovir HCl, wherein the dose is administered twice per day (BID or Q12h).

Described below are embodiments of the invention, where for convenience Embodiment 1 (E1) is identical to the embodiment provided above.

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

Brief Description of Drawing

FIG. 1 shows the results of a Phase 2 Open-Label Study in Infants with Respiratory Syncytial Virus Lower Respiratory Tract Infection, followed by a Double-blind, Placebo Controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect of RV521 (sisunatovir).

Detailed Description of the Invention

The present invention may be understood more readily by reference to the following detailed description of the embodiments of the invention and the Examples included herein. It is to be also understood that the terminology used herein is for the purpose of describing specific embodiments only and is not intended to be limiting.

E1 A method for treating RSV infection, as defined above.

E2 A method of embodiment E1, wherein the dose is from about 4.0 mg/kg to about 7 mg/kg of sisunatovir HCl.

E3 A method of embodiment E1, wherein the dose is from about 4.0 mg/kg to about 6.5 mg/kg of sisunatovir HCl.

E4 A method of embodiment E1, wherein the dose is from about 4.2 mg/kg to about 6.5 mg/kg of sisunatovir HCl.

E5 A method of embodiment E1, wherein the dose is from about 4.5 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

E6 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

E7 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

E8 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 5.5 mg/kg of sisunatovir HCl.

E9 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 5.0 mg/kg of sisunatovir HCl.

E10 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.2 mg/kg to about 4.8 mg/kg of sisunatovir HCl.

E11 A method of embodiment E1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.5 mg/kg of sisunatovir HCl.

E12 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

E13 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 4.0 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

E14 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 4.5 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

E15 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 5.0 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

E16 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 5.2 mg/kg to about 5.8 mg/kg of sisunatovir HCl.

E17 A method of embodiment E1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 5.5 mg/kg of sisunatovir HCl.

E18 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

E19 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 4.5 mg/kg to about 7 mg/kg of sisunatovir HCl.

E20 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 5.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

E21 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 5.5 mg/kg to about 6.5 mg/kg of sisunatovir HCl.

E22 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 5.7 mg/kg to about 6.3 mg/kg of sisunatovir HCl.

E23 A method of embodiment E1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 6.0 mg/kg of sisunatovir HCl.

E24 A method for treating RSV infection comprising administering to a 1- to 60-month-old subject in need thereof a total daily dose of from about 8.0 mg/kg to about 16.0 mg/kg of sisunatovir HCl.

E25 A method of embodiment E24 wherein the total daily dose is from about 8.0 mg/kg to about 13 mg/kg.

E26 A method of embodiment E24 wherein the subject is a 1- to 6-month-old and the total daily dose is from about 8 mg/kg to about 10 mg/kg.

E27 A method of embodiment E24 wherein the subject is a 6- to 12-month-old and the total daily dose is from about 10 mg/kg to about 12 mg/kg.

E28 A method of embodiment E24 wherein the subject is a 12- to 60-month-old and the total daily dose is from about 11 mg/kg to about 13 mg/kg.

E29 A method according to any of embodiments E1 to E28 and E30 to E40 wherein sisunatovir HCl is administered orally.

E30 A method according to embodiment E1 wherein the dose is about 5 mg/kg to about 6.0 of sisunatovir HCl.

E31 A method for treating RSV infection according to any of the embodiments E1 to E30 and E32 to E40 wherein the dosage of sisunatovir HCl is replaced by an equivalent dosage of sisunatovir free base.

E32 A method for treating RSV infection comprising administering to a 6- to 36-month-old subject in need thereof a dose of from about 4.0 mg/kg to about 5.5 mg/kg of sisunatovir HCl, or a pharmaceutically acceptable salt thereof, wherein the dose is administered twice per day (BID).

E33 A method of embodiment E32, wherein the dose is from about 4.0 mg/kg to about 5.0 mg/kg.

E34 A method of embodiment E32, wherein the dose is from about 4.25 mg/kg to about 5.0 mg/kg.

E35 A method of embodiment E32, wherein the dose is from about 4.25 mg/kg to about 4.75 mg/kg.

E36 A method of embodiment E32, wherein the dose is from about 4.3 mg/kg to about 4.6 mg/kg.

E37 A method of embodiment E32, wherein the dose is from about 4.4 mg/kg to about 4.6 mg/kg.

E38 A method of embodiment E32, wherein the dose is about 4.5 mg/kg.

E39 A method of any of the embodiments E1 to E38, wherein sisunatovir is administered as a single agent.

E40 A method of any of the embodiments E1 to E38, wherein sisunatovir is administered in combination with another RSV treatment.

Each of the embodiments described herein may be combined with any other embodiment(s) described herein not inconsistent with the embodiment(s) with which it is combined.

Definitions

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention have the meanings that are commonly understood by those of ordinary skill in the art.

The invention described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein.

As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" substituent includes one or more substituents.

As used herein, the term “about” when used to modify a numerically defined parameter (e.g., the dose of a sisunatovir) means that the parameter may vary by as much as 20% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg/kg means 5 mg/kg ± 20%, i.e., it may vary between 4 mg/kg and 6 mg/kg.

As used herein, the term “combination”, unless otherwise indicated, means a fixed-dose combination or a combination of agents that is administered intermittently, concurrently, or sequentially, according to the same or different route of administration and according to the same or different dosage schedules.

As used herein, the terms "treating", "treat" or "treatment", unless otherwise indicated, embraces both preventative, i.e., prophylactic, and palliative treatment, i.e., relieve, alleviate, or slow the progression of the patient’s RSV infection or any tissue damage associated with the RSV infection.

Administration and Dosing

As used herein, the phrase “effective dose” refers to the amount of sisunatovir that elicits the biological or medicinal response in the 1- to 60-month-old subject, which may include one or more of the following:

(1) preventing the disease; for example, preventing the RSV infection in a 1- to 60-month-old subject that may have been exposed to RSV but does not yet experience or display the pathology or symptomatology of the RSV infection;

(2) inhibiting the disease; for example, inhibiting the RSV infection in a 1- to 60-month-old subject that is experiencing or displaying the pathology or symptomatology of the RSV infection (i.e., arresting (or slowing) further development of the pathology or symptomatology or both); and

(3) ameliorating the disease; for example, ameliorating the pathology or symptomatology of the RSV infection (i.e., reversing the pathology or symptomatology or both).

The use of sisunatovir to treat RSV infection is administered in an amount effective to treat a condition as described herein. Sisunatovir may be administered as compound per se, or alternatively, as a pharmaceutically acceptable salt.

In one embodiment, sisunatovir may be administered as a hydrochloride salt (HCl). For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds described herein are known to one of skill in the art.

Sisunatovir may administered by any suitable route in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended.

Sisunatovir may be administered orally. Oral administration may involve swallowing, so that sisunatovir enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the bloodstream directly from the mouth.

In a preferred embodiment, the daily dose of sisunatovir or a pharmaceutically acceptable salt thereof, is administered orally twice a day.

Sisunatovir, or a pharmaceutically acceptable salt, may be present in a pharmaceutical composition which includes at least one pharmaceutically acceptable excipient. "Pharmaceutically acceptable excipient" refers to a component that may be included in the compositions described herein, is physiologically suitable for pharmaceutical use, and causes no significant adverse effects nor therapeutic effects to a subject. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The amount of sisunatovir, or a pharmaceutically acceptable salt, in the pharmaceutical compositions can be any amounts disclosed herein.

The formulation will preferably be adapted to the particular mode of administration. These compounds may be formulated with pharmaceutically acceptable excipients as known in the art and administered in a wide variety of dosage forms as known in the art. Dosage unit forms or pharmaceutical compositions suitable for oral administration include, but are not limited to tablets, capsules, such as gelatin capsules, pills, powders, granules, aqueous and nonaqueous oral solutions and suspensions, packaged in containers adapted for subdivision into individual doses.

Examples

In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

Example 1: Phase 2 Sisunatovir Clinical Trial In Pediatric Population

Overview

Sisunatovir was investigated in a Phase 2 Open-Label Study in Infants with Respiratory Syncytial Virus Lower Respiratory Tract Infection, followed by a Double-blind, Placebo Controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect of RV521 (sisunatovir).

Study Design: The overall study design is detailed in FIG. 1. The study contains two parts, Part A and Part B: To evaluate the safety and tolerability of single (Part A) and multiple (Part B) oral doses of RV521 in infants hospitalized with RSV lower respiratory tract infection (LRTI).

Selection of Starting Single Dose of Sisunatovir HCl in Pediatrics

The starting doses were estimated using a population pharmacokinetic (PK) approach according to the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) requirements (FDA CDER/CBER Guidance for Industry; EMEA/CHMP Guideline). PK data from healthy adult subjects who had received sisunatovir during clinical studies: C5241001 (formerly referenced as REVC001) and C5241002 (formerly referenced as REVC002) were used to build a population PK model using Phoenix nonlinear mixed effects (NLME) software. The model was verified using standard checks, such as Visual Predictive Check plots, bootstrap analysis, and goodness-of-fit plots (EMA, 2007), which compared the predicted concentration values to actual observed concentrations as well as showed the residual differences between predicted and actual concentrations as an assessment of model validity. The terms for allometric scaling and maturation factors in an infant population, depending on postnatal age and body weight, were added to the model to simulate PK profiles and resulting exposure in infants. The model was informed with the available demographic covariates to allow the incorporation of a nonlinear dose effect, formulation, and/or food effect, and available body weight and age data to support extrapolation to infants.

The simulated exposure was restricted by the lower bound for efficacy, using the EC90 for RSV inhibition, applied to the unbound concentration after the first dose (Dose 1) at the end of the dosing interval of 12 hours (minimum concentration [Cmin]). This equated to a total sisunatovir concentration of 7.3 ng/mL (converted from unbound). Initial target was Cmin of ~21 ng/mL in Part A. In Part B, exposure (Cmin, Cmax, and area under the curve from time zero to tau [the dosing interval] [AUCtau]) targets were comparable to 200 mg Q12h in adults. 200 mg Q12h in adults was found to be efficacious in C5241002 (viral challenge study). To assess where the upper limit of the exposure could be set, the Cmax and AUCtau for the last dose (Dose 10) of the BID dosing regimen in adult subjects dosed at 350 mg of sisunatovir (Clinical Study C5241002 [formerly referenced as REVC002])) were used as a guideline and

are presented in a separate report (Syneos Health, 2018). Therefore, the upper limit for dose levels was selected such that the peak plasma exposure levels did not exceed the group mean values observed in Clinical Study C5241002 [formerly referenced as REVC002]) (Cmax of 294 ng/mL) and total exposure (AUCtau 2500 ng×h/mL).

The resulting proposed starting doses for Part A from Phoenix NLME population PK model, Cohort 2, was 2 mg/kg for infants ≥1 month to <6 months of age and for Part A, Cohort 1, was 2.5 mg/kg for infants ≥6 months to ≤36 months of age for actual doses and dose adjustments.

Part A (single dose)

As per protocol, the first group of 3 subjects enrolled into Cohort 1 (age: ≥6 months to ≤36 months) received a single dose of 2.5 mg/kg sisunatovir suspended in pharmacopoeial-grade water administered by oral syringe. At the initial dose of 2.5 mg/kg sisunatovir suspended in pharmacopoeial-grade water, only 2 out of 3 subjects had 1 post-Dose sample collected, only 1 of which was quantifiable for sisunatovir. The third subject exhibited quantifiable concentration of sisunatovir until at least 12 hours post-Dose. The reduced number of PK samples taken from 2 subjects dosed at 2.5 mg/kg was likely due to poor palatability of sisunatovir when suspended in pharmacopoeial-grade water, which resulted in one subject being withdrawn from the study. Dose adjustments for sisunatovir in Cohort 1 were made as follows: 1.0 mg/kg. Three subjects were dosed at 1.0 mg/kg via oral syringe with sisunatovir suspended in pharmacopoeial-grade water. At the next dose level of 1.0 mg/kg sisunatovir suspended in pharmacopoeial-grade water, most of the PK samples analysed were below the limit of quantification (BLQ), except for 2 quantifiable concentrations for 1 of the 3 subjects.

Dose adjustments for sisunatovir in Cohort 1 were made as follows: and then 2.0 mg/kg. At a dose of 2.0 mg/kg suspended in formula milk for oral administration, 6 out 7 subjects had quantifiable concentrations of sisunatovir through the 6-to-8-hour post-Dose timepoint, with 2 out of 7 subjects remaining quantifiable for sisunatovir until at least 12 hours post-Dose. Approval of protocol version 4.0 and country-specific amendments permitted the use of either formula milk or breast milk as a suspending diluent for dose administration via oral syringe (pharmacopeial-grade water was still recommended for dose administration via nasogastric tube). All 7 subjects in Cohort 1 were dosed with 2.0 mg/kg via oral syringe with sisunatovir suspended in formula milk.

Subjects in Cohort 2 (age: ≥1 month to <6 months) were dosed with 2.0 mg/kg sisunatovir suspended in either formula milk or pharmacopeial-grade water depending on the route of administration. Three of the subjects were dosed via oral syringe using formula milk as the suspending diluent, and 3 were dosed via nasogastric tube using pharmacopeial-grade water as the suspending diluent.

Part B

The Phoenix NLME Population PK model was updated with data from Part A and used to predict doses for Part B. The Phoenix NLME popPK model was built with C5241001, C5241002 adult data and Part A (single dose) pediatric data from C5241003.

As per protocol, the first group of 3 subjects enrolled into Cohort 3 (age: ≥6 months to ≤36 months) received 10 doses of 2.5 mg/kg sisunatovir suspended in 0.9% weight per volume (w/v) sodium chloride (saline) administered by oral syringe.

Dose adjustments for sisunatovir in Cohort 3 was made as follows: 3.5 mg/kg, because the Phoenix NLME Population PK prediction for 2.5 mg/kg too low. Two subjects were dosed at 3.5 mg/kg via oral syringe with sisunatovir suspended in saline. One subject was dosed at 3.5 mg/kg via nasogastric tube using pharmacopoeial-grade water as the suspending diluent for doses 1-7 and via oral syringe with sisunatovir suspended in saline for doses 8-10. One subject was dosed at 3.5 mg/kg via oral syringe with sisunatovir suspended in saline for doses 1-3 and with sisunatovir suspended in formula milk for doses 4-10. Exposures from 3.5 mg/kg were too low.

Dose adjustments for sisunatovir in Cohort 3 was as follows: 5.0 mg/kg, because exposures from 3.5 mg/kg were too low. One subject was dosed at 5 mg/kg sisunatovir suspended in formula milk via oral syringe for doses 1 and 10, and via nasogastric tube for doses 2-9. One subject was dosed at 5 mg/kg via oral syringe with sisunatovir suspended in formula milk via oral syringe.

Table 1 below compares key simulation data for pediatric patients aged 1 to 6 months, 6 to 12 months, and 12 to 60 months from a NONMEM population pharmacokinetic model to data from sisunatovir studies in adults (DeVincenzo et al.). The table included values obtained for steady-state trough concentration (CtroughSS), steady-state maximum concentration (CmaxSS), and area under the curve from time zero to time tau (the dosing interval) (AUCtauSS) predicted to achieve a comparable exposure to adults receiving 200 mg twice daily. Therefore, seeking at least an equivalent exposure as in the adult study, at least 4.5 mg/kg is the predicted appropriate dosage for 1- to 6-month-old patients BID (twice daily), at least 5.5 mg/kg is the predicted appropriate dosage for 6- to 12-month-old patients BID (twice daily), and at least 6 mg/kg is predicted appropriate dosage for 12- to 60-month-old patients BID (twice daily). Doses could increase up to the limit of impurity specification (8 mg/kg BID [twice daily]).

TABLE 1

Age (month)	Predicted Dose (mg/kg)	$AUCtau_{SS}$	C_{maxSS}	$C_{troughSS}$
		Geomean	Geomean	Geomean
1-6	4.5	808 (1.4-fold)	139 (1.6-fold)	43 (1.1-fold)
6-12	5.5	716 (1.3-fold)	129 (1.5-fold)	40 (1.1-fold)
12-60	6.0	643 (1.1-fold)	118 (1.4-fold)	38 (1-fold)
Adult	200 mg flat-dose	560	87	38
Note: predictions in exposures derived from population PK model to target at least comparable exposure to adults receiving 200 mg twice-daily. Doses could increase up to the limit of impurity specification (8 mg/kg BID [twice daily]). Abbreviations: AUCtauss, steady-state area under the concentration-time curve from time zero to time tau (the dosing interval); CmaxSS, steady-state maximum concentration; CtroughSS, steady-state trough concentration (prior to dosing); Geomean, geometric mean.				

After the completion of C5241003, a population PK model was developed using non-linear mixed-effect modeling (NONMEM) software that include a CYP3A4 maturation. This refined NONMEM population PK model included data from C5241001, C5241002, C5241003, and C5241006. This NONMEM population PK model was used to simulate pediatric exposures across a range of ages and weight-based dosing to identify doses that were predicted to have exposures at least comparable to adults receiving 200 mg twice-daily (Table 1). Pediatric doses were targeting exposures greater than or equal to 200 mg Q12h (twice daily, every 12 hours) in adults ($C_{troughSS}$ 38 ng/mL, C_{maxSS} 87 ng/mL, AUC_{tauSS} 561 h.ng/mL).

Thus, based on the results of Part B, it was unexpectedly discovered that pediatric patients 1- to 60-months of age will require a much higher dosing compared to what was initially expected. It was found that dosing in pediatric patients aged 1 to 6 months would require at least 4.5 mg/kg, pediatric patients aged 6 to 12 months would require at least 5.5 mg/kg, pediatric patients 12 to 60 months would require at least 6 mg/kg twice daily (BID). These pediatric patients should receive a weight-based dose until the calculated dose is equal to the adult flat dose of 200 mg in adults. Based on standard growth charts it is anticipated that most adolescents will receive the adult flat dose.

CLAIMS

We claim:

1. A method for treating RSV infection comprising administering to a 1- to 60-month-old subject in need thereof a dose of from about 4.0 mg/kg to about 8.0 mg/kg of sisunatovir HCl, wherein the dose is administered twice per day (BID).

2. The method of claim 1, wherein the dose is from about 4.5 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

3. The method of claim 1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

4. The method of claim 1, wherein the subject is a 1- to 6-month-old and wherein the dose is from about 4.0 mg/kg to about 5.0 mg/kg of sisunatovir HCl.

5. The method of claim 1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

6. The method of claim 1, wherein the subject is a 6- to 12-month-old and wherein the dose is from about 5.0 mg/kg to about 6.0 mg/kg of sisunatovir HCl.

7. The method of claim 1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 4.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

8. The method of claim 1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 5.0 mg/kg to about 7.0 mg/kg of sisunatovir HCl.

9. The method of claim 1, wherein the subject is a 12- to 60-month-old and wherein the dose is from about 5.5 mg/kg to about 6.5 mg/kg of sisunatovir HCl.

10. The method of claim 1, wherein sisunatovir HCl is administered orally.

11. A method for treating RSV infection comprising administering to a 1- to 60-month-old subject in need thereof a total daily dose of from about 8.0 mg/kg to about 16.0 mg/kg of sisunatovir HCl.

12. The method of claim 11, wherein the total daily dose is from about 8.0 mg/kg to about 13 mg/kg.

13. The method of claim 11, wherein the subject is a 1- to 6-month-old and the total daily dose is from about 8 mg/kg to about 10 mg/kg.

14. The method of claim 11, wherein the subject is a 6- to 12-month-old and the total daily dose is from about 10 mg/kg to about 12 mg/kg.

15. The method of claim 11, wherein the subject is a 12- to 60-month-old and the total daily dose is from about 11 mg/kg to about 13 mg/kg.

16. The method of claim 11, wherein sisunatovir HCl is administered orally.

FIG. 1

Clinical Trial Results:
A Phase 2 Open-Label Study in Infants with Respiratory Syncytial Virus Lower Respiratory Tract Infection, Followed by a Double-blind, Placebo Controlled Part, to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Effect of RV521 (REVIRAL 1)

Summary	
EudraCT number	2018-001010-15
Trial protocol	HU BE PL
Global end of trial date	05 Dec 2022
Results information	
Results version number	v1(current)
This version publication date	-
First version publication date	-
Other versions	

Trial information	
Trial identification	
Sponsor protocol code	C5241003
Additional study identifiers	
ISRCTN number	-
US NCT number	NCT04225897
WHO universal trial number (UTN)	-
Other trial identifiers	REVC003: Study ID
Sponsors	
Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
Results analysis stage	
Analysis stage	Final
Date of interim/final analysis	27 Jan 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 Dec 2022
Was the trial ended prematurely?	Yes
General information about the trial	
Main objective of the trial	Part A and Part B: 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).
Protection of trial subjects	The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.
Background therapy	-

Evidence for comparator	-
Actual start date of recruitment	13 Nov 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes
Population of trial subjects	
Number of subjects enrolled per country	
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	Panama: 3
Country: Number of subjects enrolled	Spain: 27
Worldwide total number of subjects	51
EEA total number of subjects	31
Number of subjects enrolled per age group	
In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	43
Children (2-11 years)	8
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0
Subject disposition	
Recruitment	
Recruitment details	-
Pre-assignment	
Screening details	This study was planned to be conducted in 3 parts: Part A, B and optional part C. Part C was not conducted as part of a reassessment of the clinical development plan for RV521 (sisunatovir); hence, data is not reported for Part C in any section of the results. A total of 51 subjects were enrolled in the study (Part A=19 and Part B=32).

Period 1	
Period 1 title	Part A (Screening Visit to Day 7)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive	Yes
Arm title	Cohort 1: RV521 1.0 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 1.0 milligram per kilogram (mg/kg) of RV521 orally on Day 1.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details	Subjects were administered RV521 1.0 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route on Day 1.
Arm title	Cohort 1: RV521 2.0 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.0 mg/kg of RV521 orally on Day 1.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 2.0 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route on Day 1.
Arm title	Cohort 1: RV521 2.5 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.5 mg/kg of RV521 orally on Day 1.
Arm type	Experimental
Investigational medicinal product name	RV521

Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 2.5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route on Day 1.
Arm title	Cohort 2: RV521 2.0 mg/kg
Arm description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received a single dose of 2 mg/kg of RV521 orally on Day 1.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 2.0 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route on Day 1.

Number of subjects in period 1 [1]	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Started	3	7	3	6
Completed	3	6	1	6
Not completed	0	1	2	0
Adverse events	-	1	-	-
Parent/legal guardian request	-	-	1	-
Lost to follow-up	-	-	1	-

Notes
[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Total 51 subjects were enrolled (Part A=19 and Part B=32).

Period 2	
Period 2 title	Part B (Screening Visit to Day 12)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms	
Are arms mutually exclusive	No
Arm title	Cohort 3: Placebo
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received placebo every 12 hours twice daily (BID) orally for 5 days.
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered placebo dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of placebo separated by 12 hours orally for 5 days.
Arm title	Cohort 3: RSV1 2.5 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Arm type	Experimental

Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 2.5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of RV521 separated by 12 hours orally for 5 days.
Arm title	Cohort 3: RV521 3.5 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 3.5 mg/kg every 12 hours (BID) orally for 5 days.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details	Subjects were administered RV521 3.5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of RV521 separated by 12 hours orally for 5 days.
Arm title	Cohort 3: RV521 5 mg/kg
Arm description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 5 mg/kg every 12 hours (BID) orally for 5 days.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of RV521 separated by 12 hours orally for 5 days.
Arm title	Cohort 4: Placebo
Arm description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered placebo dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of placebo separated by 12 hours orally for 5 days.
Arm title	Cohort 4: RV521 2.5 mg/kg
Arm description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Arm type	Experimental
Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details	Subjects were administered RV521 2.5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of RV521 separated by 12 hours orally for 5 days.
Arm title	Cohort 5: Placebo
Arm description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered placebo dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of placebo separated by 12 hours orally for 5 days.
Arm title	Cohort 5: RV521 2.5 mg/kg
Arm description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Arm type	Experimental

Investigational medicinal product name	RV521
Investigational medicinal product code	
Other name	Sisunatovir
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details	Subjects were administered RV521 2.5 mg/kg dispersed in a defined volume of permitted suspending diluent via the oral route. Subjects received BID of RV521 separated by 12 hours orally for 5 days.

Number of subjects in period 2	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Started	3	3	4	3	1	4	6	8
Completed	3	3	4	2	1	4	6	8
Not completed	0	0	0	1	0	0	0	0
Parent/legal guardian request	-	-	-	1	-	-	-	-

Baseline characteristics

Baseline characteristics reporting groups	
Reporting group title	Cohort 1: RV521 1.0 mg/kg

Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 1.0 milligram per kilogram (mg/kg) of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.0 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.0 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.5 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 2: RV521 2.0 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received a single dose of 2 mg/kg of RV521 orally on Day 1.

Reporting group values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg	Total
Number of subjects	3	7	3	6	19
Age Categorical					
Units: Subjects					
Infants and toddlers (28 days-23 months)	1	5	3	6	15
Children (2-11 years)	2	2	0	0	4

Age Continuous					
99999 indicates standard deviation could not be calculated as a single subject was analysed.					
Units: months					
arithmetic mean (standard deviation)	27.8 ± 5.90	18.1 ± 7.25	9.4 ± 2.46	2.7 ± 1.69	-
Gender Categorical					
Units: Subjects					
Female	0	4	2	1	7
Male	3	3	1	5	12
Race					
Units: Subjects					
American Indian or Alaskan Native	0	0	0	1	1
Asian	0	7	0	1	8
White	3	0	3	4	10
Black or African American	0	0	0	0	0
Unknown or Other	0	0	0	0	0
Ethnicity					

Units: Subjects					
Hispanic or Latino	0	0	3	1	4
Not Hispanic or Latino	3	7	0	5	15
Unknown	0	0	0	0	0

Subject analysis sets	
Subject analysis set title	Cohort 3: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 3: RSV1 2.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 3: RV521 3.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 3.5 mg/kg every 12 hours (BID) orally for 5 days.

Subject analysis set title	Cohort 3: RV521 5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4: RV521 2.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 5: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 5: RV521 2.5 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4 and 5 combined: RV521 2.5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received BID of RV521 2.5 mg/kg separated by 12 hours orally for 5 days. Subjects from Cohort 4 and 5 were included.
Subject analysis set title	Cohort 4 and 5 combined: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received BID of placebo separated by 12 hours orally for 5 days. Subjects from Cohorts 4 and 5 were included.

Subject analysis sets values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg	Cohort 4 and 5 combined: RV521 2.5 mg/kg	Cohort 4 and 5 combined: Placebo
Number of subjects	3	3	4	3	1	4	5	8	12	6
Age Categorical										
Units: Subjects										
Infants and toddlers (28 days-23 months)	3	3	2	1	1	4	5	8	12	6
Children (2-11 years)	0	0	2	2	0	0	0	0	0	0

Age Continuous										
99999 indicates standard deviation could not be calculated as a single subject was analysed.										
Units: months										
arithmetic mean (standard deviation)	17.5 ± 4.00	8.9 ± 4.51	18.5 ± 13.54	22.2 ± 7.97	1.6 ± 99999	1.2 ± 0.43	2.0 ± 0.47	3.0 ± 1.10	2.4 ± 1.26	1.9 ± 0.45
Gender Categorical										
Units: Subjects										
Female	1	1	3	2	0	0	0	5	5	0
Male	2	2	1	1	1	4	5	3	7	6
Race										
Units: Subjects										
American Indian or Alaskan Native	1	0	0	0	0	0	0	1	1	0
Asian	1	3	1	1	0	0	1	1	1	1
White	1	0	3	1	1	4	2	6	10	3
Black or African American	0	0	0	0	0	0	1	0	0	1
Unknown or Other	0	0	0	1	0	0	1	0	0	1

Ethnicity										
Units: Subjects										
Hispanic or Latino	1	0	0	0	0	1	2	1	2	2
Not Hispanic or Latino	2	3	4	3	1	3	2	7	10	3
Unknown	0	0	0	0	0	0	1	0	0	1

End points	
End points reporting groups	
Reporting group title	Cohort 1: RV521 1.0 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 1.0 milligram per kilogram (mg/kg) of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.0 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.0 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.5 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 2: RV521 2.0 mg/kg

Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received a single dose of 2 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 3: Placebo
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received placebo every 12 hours twice daily (BID) orally for 5 days.
Reporting group title	Cohort 3: RSV1 2.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 3: RV521 3.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 3.5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 3: RV521 5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 4: Placebo
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 4: RV521 2.5 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.

Reporting group title	Cohort 5: Placebo
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 5: RV521 2.5 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 3: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 3: RSV1 2.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 3: RV521 3.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 3.5 mg/kg every 12 hours (BID) orally for 5 days.

Subject analysis set title	Cohort 3: RV521 5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4: RV521 2.5 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 5: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 5: RV521 2.5 mg/kg
Subject analysis set type	Safety analysis

Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Subject analysis set title	Cohort 4 and 5 combined: RV521 2.5 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received BID of RV521 2.5 mg/kg separated by 12 hours orally for 5 days. Subjects from Cohort 4 and 5 were included.
Subject analysis set title	Cohort 4 and 5 combined: Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received BID of placebo separated by 12 hours orally for 5 days. Subjects from Cohorts 4 and 5 were included.
Primary: Part A: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Withdrawals due to TEAEs	
End point title	Part A: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Withdrawals due to TEAEs [1]
End point description	An adverse event (AE) was defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which did not necessarily have a causal relationship with the investigational medicinal product (IMP). TEAEs were defined as AEs which started, or worsened, after the first dose of IMP. An SAE was any untoward medical occurrence or effect that, at any dose, resulted in death; was life threatening; required or prolonged inpatient hospitalisation; resulted in persistent or significant disability/incapacity or other important medical event. Safety population included all subjects who received at least 1 dose of IMP.

End point type	Primary
End point timeframe	From start of IMP on Day 1 up to Day 7
Notes [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects				
TEAEs	2	5	3	1
SAEs	0	1	0	0
Withdrawals due to TEAEs	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Withdrawals due to TEAEs

End point title	Part B: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Withdrawals due to TEAEs [2]
End point description	An AE was defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which did not necessarily have a causal relationship with the IMP. TEAEs were defined as AEs which started, or worsened,

	after the first dose of IMP. An SAE was any untoward medical occurrence or effect that, at any dose, resulted in death; was life threatening; required or prolonged inpatient hospitalisation; resulted in persistent or significant disability/incapacity or other important medical event. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	From start of IMP on Day 1 up to Day 12

Notes
[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	1	4	5	8
Units: Subjects								
TEAEs	1	2	1	1	1	2	3	1
SAEs	0	0	0	0	0	0	0	0
Withdrawal due to TEAEs	0	0	0	1	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at Baseline

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at Baseline [3]
End point description	Physical examination included general appearance; head, eyes, ears, nose and throat (HEENT); dermatologic; cardiovascular; respiratory; gastrointestinal; and neurological examination. Clinical significance of results were determined by the investigator. Safety population included all subjects who received at least 1 dose of IMP. Here, 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects				
General appearance; n=3,7,3,5	0	1	0	0
HEENT; n=3,7,3,4	1	2	0	0
Dermatologic; n=3,7,3,4	0	0	0	0
Cardiovascular; n=3,7,3,5	0	1	0	0

Respiratory; n=3,7,3,5	3	6	2	1
Gastrointestinal; n=3,7,3,5	0	0	0	0
Neurological; n=3,7,3,5	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results Anytime Between 18 to 24 Hours Post-dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results Anytime Between 18 to 24 Hours Post-dose [4]
End point description	Physical examination included general appearance; HEENT; dermatologic; cardiovascular; respiratory; gastrointestinal; and neurological examination. Clinical significance of results were determined by the investigator. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Anytime between 18 to 24 hours post-dose on Day 1

Notes
[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects				
General appearance; n=3,6,2,6	0	0	0	0
HEENT; n=3,6,1,5	1	2	0	0
Dermatologic; n=3,6,1,5	0	0	0	0
Cardiovascular; n=3,6,2,6	0	0	0	0
Respiratory; n=3,6,2,6	1	4	1	1
Gastrointestinal; n=3,6,2,6	0	0	0	0
Neurological; n=3,6,2,6	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at 48 Hours Post-dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at 48 Hours Post-dose [5]
End point description	Physical examination included general appearance; HEENT; dermatologic; cardiovascular; respiratory; gastrointestinal; and neurological examination. Clinical significance of results were determined by the investigator. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects

	Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	At 48 hours post-dose on Day 1

Notes
[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects				
General appearance; n=3,6,2,6	0	0	0	0
HEENT; n=3,6,2,5	1	1	1	0
Dermatologic; n=3,6,2,5	0	0	0	0
Cardiovascular; n=3,6,2,6	0	0	0	0
Respiratory; n=3,6,2,6	1	3	1	1
Gastrointestinal; n=3,6,2,6	0	0	0	0
Neurological; n=3,6,2,6	0	0	0	0

No statistical analyses for this end point	
Primary: Part B: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at Baseline	
End point title	Part B: Number of Subjects With Abnormal Clinically Significant Physical Examination Results at Baseline [6]
End point description	Physical examination included general appearance; dermatologic; cardiovascular; respiratory; gastrointestinal; and neurological examination. Clinical significance of results were determined by the investigator. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)
Notes [6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.	

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	2	3	4	3	1	4	5	7
Units: Subjects								
General Appearance; n=2,3,4,3,1,4,5,7	0	0	1	0	0	0	0	1

HEENT; n=2,3,3,3,1,4,5,7	0	0	1	1	0	0	0	0
Dermatologic; n=2,3,4,3,1,4,5,7	0	0	0	0	0	0	0	0
Cardiovascular; n=2,3,4,3,1,4,5,7	0	0	1	0	0	0	0	0
Respiratory; n=2,3,4,3,1,4,5,7	1	2	3	3	1	2	4	3
Gastrointestinal; n=2,3,4,3,1,4,5,7	0	0	0	0	0	0	0	0
Neurological; n=2,3,4,3,1,4,5,7	0	0	1	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Physical Examination Results Anytime Between 40 to 48 Hours Post-dose 10

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Physical Examination Results Anytime Between 40 to 48 Hours Post-dose 10 [7]
End point description	Physical examination included general appearance; HEENT; dermatologic; cardiovascular; respiratory; gastrointestinal; and neurological examination. Clinical significance of results were determined by the investigator. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5

Notes
[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	0 [8]	4	5	8
Units: Subjects								
General appearance; n=3,3,4,2,0,4,5,8	0	0	0	0		0	0	0
HEENT; n=3,3,3,2,0,4,5,8	0	0	1	0		0	0	0
Dermatologic; n=3,3,3,2,0,4,5,8	0	0	0	0		0	0	0
Cardiovascular; n=3,3,3,2,0,4,5,8	0	0	0	0		0	0	0
Respiratory; n=3,3,4,2,0,4,5,8	0	1	0	0		1	0	0
Gastrointestinal; n=3,3,3,2,0,4,5,8	0	0	0	0		0	0	0
Neurological; n=3,3,3,2,0,4,5,8	0	0	0	0		0	0	0

Notes
[8] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Baseline

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Baseline [9]

End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects	0	2	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose [10]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this

	outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose on Day 1

Notes
[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects	0	1	1	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at 12 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at 12 Hours Post-Dose [11]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Primary
End point timeframe	12 hours post-dose on Day 1
Notes [11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	2	6
Units: Subjects	0	2	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 18 to 24 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 18 to 24 Hours Post-Dose [12]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary

End point timeframe	Anytime between 18 to 24 hours post-dose on Day 1
Notes [12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects	0	2	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at 48 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at 48 Hours Post-Dose [13]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	48 hours post-dose on Day 1

Notes
[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects	0	1	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Vital Signs per Investigator's Interpretation at Baseline

End point title	Part B: Number of Subjects With Abnormal Vital Signs per Investigator's Interpretation at Baseline [14]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	1	4	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 1

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 1 [15]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose 1 (Day 1)

Notes
[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	1	4	5	8
Units: Subjects	1	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation At Pre-dose 2

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation At Pre-dose 2 [16]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 2 (Day 1)

Notes
[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	1	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 3

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 3 [17]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 3 (Day 2)

Notes
[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 4

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 4 [18]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 4 (Day 2)

Notes
[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	1	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 5

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 5 [19]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 5 (Day 3)

Notes
[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	1	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 6

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 6 [20]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 6 (Day 3)

Notes
[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	3	4	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 6

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 6 [21]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose 6 (Day 3)

Notes
[21] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	4	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 7

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 7 [22]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 7 (Day 4)

Notes
[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	3	5	8
Units: Subjects	0	1	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 8

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 8 [23]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 8 (Day 4)

Notes
[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	2	2	2	1	3	4	6
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 9

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 9 [24]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 9 (Day 5)

Notes
[24] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	2	2	1	1	3	4	5
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 10

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation at Pre-dose 10 [25]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 10 (Day 5)

Notes
[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	2	1	1	1	3	4	4
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 40 to 48 Hours Post-Dose 10

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Vital Signs per Investigator's Interpretation Anytime Between 40 to 48 Hours Post-Dose 10 [26]
End point description	Vital signs included body temperature, systolic and diastolic blood pressure, respiratory rate, heart rate and pulse oximetry. Number of subjects with abnormal clinically significant vital signs per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5

Notes
[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	0 [27]	4	5	8
Units: Subjects	0	0	0	0		0	0	0

Notes
[27] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Hematology Results at Baseline

End point title	Part A: Number of Subjects With Abnormal Hematology Results at Baseline [28]
End point description	Haematology parameters included basophils, eosinophils, lymphocytes, monocytes, neutrophils, haemoglobin (Hb), haematocrit (HCT), white blood cell count (WBC), red blood cell count (RBC), platelet count, mean cell volume (MCV), mean cell haemoglobin (MCH), and MCH concentration (MCHC). Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

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

end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	2	7	3	6
Units: Subjects				
Basophils; below normal range; n=2,7,1,6	0	0	0	0
Basophils; above normal range; n=2,7,1,6	0	0	0	0
Eosinophils; below normal range; n=2,7,1,6	0	0	0	0
Eosinophils; above normal range; n=2,7,1,6	0	0	0	0
MCHC; below normal range; n=2,7,1,6	0	0	0	0
MCHC; above normal range; n=2,7,1,6	0	0	0	0
MCH; below normal range; n=2,7,1,6	0	0	0	0
MCH; above normal range; n=2,7,1,6	0	0	0	0
MCV; below normal range; n=2,7,1,6	0	0	0	0
MCV; above normal range; n=2,7,1,6	0	0	0	0
RBC; below normal range; n=2,7,1,6	0	0	0	0

RBC; above normal range; n=2,7,1,6	0	0	0	0
HCT; below normal range; n=2,7,1,6	0	0	0	0
HCT; above normal range; n=2,7,1,6	0	0	0	0
Hb; below normal range; n=2,7,3,6	0	0	1	0
Hb; above normal range; n=2,7,3,6	0	0	0	0
WBC; below normal range; n=2,7,1,6	0	0	1	1
WBC; above normal range; n=2,7,1,6	0	0	0	0
Lymphocytes; below normal range; n=2,7,1,6	0	0	0	0
Lymphocytes; above normal range; n=2,7,1,6	0	0	0	0
Monocytes; below normal range; n=2,7,1,6	0	0	0	0
Monocytes; above normal range; n=2,7,1,6	0	0	0	0
Neutrophils; below normal range; n=2,7,1,6	0	0	0	0
Neutrophils; above normal range; n=2,7,1,6	0	0	0	0
Platelets; below normal range; n=2,7,1,6	0	2	0	1
Platelets; above normal range; n=2,7,1,6	0	0	0	1
No statistical analyses for this end point				

Primary: Part A: Number of Subjects With Abnormal Hematology Results at 48 Hours Post-Dose	
End point title	Part A: Number of Subjects With Abnormal Hematology Results at 48 Hours Post-Dose [29]
End point description	Haematology parameters included basophils, eosinophils, lymphocytes, monocytes, neutrophils, Hb, HCT, WBC, RBC, platelet count, MCV, MCH and MCHC. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	48 hours post-dose on Day 1
Notes [29] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	5
Units: Subjects				
Basophils; below normal range; n=3,6,1,5	0	0	0	0
Basophils; above normal range; n=3,6,1,5	0	0	0	0
Eosinophils; below normal range; n=3,6,1,5	0	0	0	0

Eosinophils; above normal range; n=3,6,1,5	0	0	0	0
MCHC; below normal range; n=3,6,1,5	0	0	0	0
MCHC; above normal range; n=3,6,1,5	0	0	0	0
MCH; below normal range; n=3,6,1,5	0	0	0	0
MCH; above normal range; n=3,6,1,5	0	0	0	0
MCV; below normal range; n=3,6,1,5	0	0	0	0
MCV; above normal range; n=3,6,1,5	0	0	0	0
RBC; below normal range; n=3,6,1,5	0	0	0	0
RBC; above normal range; n=3,6,1,5	0	0	0	0
HCT; below normal range; n=3,6,1,5	0	0	0	0
HCT; above normal range; n=3,6,1,5	0	0	0	0
Hb; below normal range; n=3,6,2,5	0	0	0	0
Hb; above normal range; n=3,6,2,5	0	0	0	0
WBC; below normal range; n=3,6,1,5	0	0	0	0
WBC; above normal range; n=3,6,1,5	0	0	0	1
Lymphocytes; below normal range; n=3,6,1,5	0	0	0	0

Lymphocytes; above normal range; n=3,6,1,5	0	0	0	0
Monocytes; below normal range; n=3,6,1,5	0	0	0	0
Monocytes; above normal range; n=3,6,1,5	0	0	0	0
Neutrophils; below normal range; n=3,6,1,5	0	0	0	0
Neutrophils; above normal range; n=3,6,1,5	0	0	0	0
Platelets; below normal range; n=3,6,1,5	0	1	0	0
Platelets; above normal range; n=3,6,1,5	1	1	1	1

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Hematology Results at Baseline

End point title	Part B: Number of Subjects With Abnormal Hematology Results at Baseline [30]
End point description	Haematology parameters included basophils, eosinophils, lymphocytes, monocytes, neutrophils, Hb, HCT, WBC, RBC, platelet count, MCV, MCH and MCHC. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

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

end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	3	1	0 [31]	4	2	7
Units: Subjects								
Basophils; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Basophils; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Eosinophils; below normal range; n=3,3,3,1,0,4,2,7	1	0	1	0		0	0	2
Eosinophils; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
MCHC; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	1
MCHC; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
MCH; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	1
MCH; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
MCV; below normal range; n=3,3,3,1,0,4,2,7	0	0	1	0		0	0	0
MCV; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
RBC; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0

RBC; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
HCT; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	1		0	2	0
HCT; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Hb; below normal range; n=3,3,3,1,0,4,2,7	0	0	1	0		0	1	1
Hb; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
WBC; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		2	1	0
WBC; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Lymphocytes; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	1	0
Lymphocytes; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Monocytes; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	1
Monocytes; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	1	1
Neutrophils; below normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Neutrophils; above normal range; n=3,3,3,1,0,4,2,7	0	0	0	0		0	0	0
Platelets; below normal range; n=3,3,3,1,0,3,2,7	1	0	1	0		0	0	0
Platelets; above normal range; n=3,3,3,1,0,3,2,7	1	0	0	0		0	0	1

Notes
[31] - No subjects were evaluable

No statistical analyses for this end point	
Primary: Part B: Number of Subjects With Abnormal Hematology Results Anytime Between 40 to 48 Hours Post-dose 10	
End point title	Part B: Number of Subjects With Abnormal Hematology Results Anytime Between 40 to 48 Hours Post-dose 10 [32]
End point description	Haematology parameters included basophils, eosinophils, lymphocytes, monocytes, neutrophils, Hb, HCT, WBC, RBC, platelet count, MCV, MCH and MCHC. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5
Notes [32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.	

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	2	4	2	0 [33]	1	3	7
Units: Subjects								
Basophils; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0

Basophils; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
Eosinophils; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
Eosinophils; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
MCHC; below normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	1
MCHC; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	1		0	0	0
MCH; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	1		0	0	1
MCH; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
MCV; below normal range; n=3,2,4,2,0,1,3,7	0	0	1	1		0	0	0
MCV; above normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	0
RBC; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
RBC; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
HCT; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	2	0
HCT; above normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	0
Hb; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	1
Hb; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	1	0
WBC; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	1	1

WBC; above normal range; n=3,2,4,2,0,1,3,7	1	0	0	0		0	0	0
Lymphocytes; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	1
Lymphocytes; above normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	0	0
Monocytes; below normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	1
Monocytes; above normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	1
Neutrophils; below normal range; n=3,2,4,2,0,1,3,7	0	0	0	0		0	1	1
Neutrophils; above normal range; n=3,2,4,2,0,1,3,7	0	0	1	0		0	1	0
Platelets; below normal range; n=3,2,3,1,0,1,3,7	0	0	0	0		0	0	0
Platelets; above normal range; n=3,2,3,1,0,1,3,7	2	1	2	0		0	2	6

Notes
[33] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinical Chemistry Results at Baseline

End point title	Part A: Number of Subjects With Abnormal Clinical Chemistry Results at Baseline [34]
End point description	Clinical chemistry parameters included creatinine, urea (or blood urea nitrogen), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, and calcium. Institutional laboratory normal ranges were used. Safety population

	included all subjects who received at least 1 dose of IMP. Here, 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)
Notes [34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects				
ALT; below normal range; n=3,7,3,5	0	0	0	0
ALT; above normal range; n=3,7,3,5	0	0	0	0
Albumin; below normal range; n=3,7,3,6	0	0	0	0
Albumin; above normal range; n=3,7,3,6	0	0	0	0
ALP; below normal range; n=3,7,3,5	0	0	0	0
ALP; above normal range; n=3,7,3,5	0	0	0	0
AST; below normal range; n=3,7,3,5	0	0	0	0

AST; above normal range; n=3,7,3,5	0	0	0	0
Bilirubin; below normal range; n=3,7,3,6	0	0	0	0
Bilirubin; above normal range; n=3,7,3,6	0	0	0	0
Calcium; below normal range; n=3,7,3,6	0	1	0	0
Calcium; above normal range; n=3,7,3,6	0	0	0	1
Chloride; below normal range; n=3,7,3,6	0	0	0	0
Chloride; above normal range; n=3,7,3,6	0	0	0	0
Creatinine; below normal range; n=3,7,3,6	0	0	0	0
Creatinine; above normal range; n=3,7,3,6	0	0	0	0
GGT; below normal range; n=3,7,3,5	0	0	0	0
GGT; above normal range; n=3,7,3,5	0	0	0	0
Glucose; below normal range; n=3,7,3,6	0	0	0	0
Glucose; above normal range; n=3,7,3,6	0	0	0	0
LDH; below normal range; n=3,7,3,3	0	0	0	0
LDH; above normal range; n=3,7,3,3	0	0	0	0
Potassium; below normal range; n=3,7,3,4	0	0	0	0

Potassium; above normal range; n=3,7,3,4	0	0	0	1
Protein; below normal range; n=3,7,3,6	0	0	0	0
Protein; above normal range; n=3,7,3,6	0	0	0	0
Sodium; below normal range; n=3,7,3,6	0	1	0	0
Sodium; above normal range; n=3,7,3,6	0	0	0	0
Urea; below normal range; n=3,7,3,6	0	0	0	0
Urea; above normal range; n=3,7,3,6	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinical Chemistry Results at 48 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinical Chemistry Results at 48 Hours Post-Dose [35]
End point description	Clinical chemistry parameters included creatinine, urea, AST, ALT, GGT, ALP, LDH, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, and calcium. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	48 hours post-dose on Day 1

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

end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects				
ALT; below normal range; n=3,6,1,5	0	0	0	0
ALT; above normal range; n=3,6,1,5	0	0	0	0
Albumin; below normal range; n=3,6,1,5	0	0	0	0
Albumin; above normal range; n=3,6,1,5	0	0	0	0
ALP; below normal range; n=3,6,1,5	0	0	0	0
ALP; above normal range; n=3,6,1,5	0	0	0	0
AST; below normal range; n=3,5,1,5	0	0	0	0
AST; above normal range; n=3,5,1,5	0	0	0	0
Bilirubin; below normal range; n=3,6,1,5	0	0	0	0
Bilirubin; above normal range; n=3,6,1,5	0	0	0	0
Calcium; below normal range; n=3,6,1,5	0	0	0	0

Calcium; above normal range; n=3,6,1,5	0	0	0	1
Chloride; below normal range; n=3,6,1,5	0	0	0	0
Chloride; above normal range; n=3,6,1,5	0	0	0	0
Creatinine; below normal range; n=3,6,1,4	0	0	0	0
Creatinine; above normal range; n=3,6,1,4	0	0	0	0
GGT; below normal range; n=3,6,1,5	0	0	0	0
GGT; above normal range; n=3,6,1,5	0	0	0	0
Glucose; below normal range; n=3,6,1,4	0	0	0	1
Glucose; above normal range; n=3,6,1,4	0	0	0	0
LDH; below normal range; n=3,5,1,5	0	0	0	0
LDH; above normal range; n=3,5,1,5	0	0	0	0
Potassium; below normal range; n=3,5,1,4	0	0	0	0
Potassium; above normal range; n=3,5,1,4	0	1	0	3
Protein; below normal range; n=3,6,1,5	0	0	0	0
Protein; above normal range; n=3,6,1,5	0	0	0	0
Sodium; below normal range; n=3,6,1,5	0	0	0	0

Sodium; above normal range; n=3,6,1,5	0	0	0	0
Urea; below normal range; n=3,6,1,5	0	0	0	0
Urea; above normal range; n=3,6,1,5	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinical Chemistry Results at Baseline

End point title	Part B: Number of Subjects With Abnormal Clinical Chemistry Results at Baseline [36]
End point description	Clinical chemistry parameters included creatinine, urea, AST, ALT, GGT, ALP, LDH, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, and calcium. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'n' signifies number of subjects evaluable for the specified categories. 99999 indicates data was not available as no subjects were evaluable.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[36] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	1	4	5	8

Units: Subjects								
ALT; below normal range; n=3,3,4,3,0,4,5,8	0	0	0	0	99999	0	0	0
ALT; above normal range; n=3,3,4,3,0,4,5,8	0	0	0	0	99999	0	0	3
Albumin; below normal range; n=2,3,3,3,1,4,4,8	0	0	0	1	0	0	1	0
Albumin; above normal range; n=2,3,3,3,1,4,4,8	0	0	0	0	0	0	0	1
ALP; below normal range; n=2,3,3,3,1,4,4,5	0	0	0	0	0	0	0	0
ALP; above normal range; n=2,3,3,3,1,4,4,5	0	0	0	0	0	0	0	0
AST; below normal range; n=3,3,4,3,0,4,5,7	0	0	0	0	99999	0	0	0
AST; above normal range; n=3,3,4,3,0,4,5,7	0	0	0	0	99999	0	0	0
Bilirubin; below normal range; n=3,3,4,3,1,4,4,8	1	0	2	1	0	0	0	2
Bilirubin; above normal range; n=3,3,4,3,1,4,4,8	0	0	0	0	0	0	0	0
Calcium; below normal range; n=2,3,2,3,1,4,3,6	0	0	0	0	0	0	0	1
Calcium; above normal range; n=2,3,2,3,1,4,3,6	0	0	0	0	0	0	0	1
Chloride; below normal range; n=3,3,4,3,1,4,5,8	1	0	0	0	0	0	0	0
Chloride; above normal range; n=3,3,4,3,1,4,5,8	0	0	0	0	0	0	0	0
Creatinine; below normal range; n=3,3,4,3,1,4,5,8	1	0	2	2	0	0	1	4

Creatinine; above normal range; n=3,3,4,3,1,4,5,8	0	0	0	0	0	0	0	0
GGT; below normal range; n=2,3,4,3,1,4,4,8	0	0	0	0	0	0	0	0
GGT; above normal range; n=2,3,4,3,1,4,4,8	0	0	0	0	0	0	0	0
Glucose; below normal range; n=3,3,4,3,1,4,4,8	0	0	0	0	0	0	0	0
Glucose; above normal range; n=3,3,4,3,1,4,4,8	1	0	3	0	0	1	0	4
LDH; below normal range; n=0,3,2,3,0,2,2,3	99999	0	0	0	99999	0	0	0
LDH; above normal range; n=0,3,2,3,0,2,2,3	99999	0	0	1	99999	0	0	0
Potassium; below normal range; n=1,3,3,3,0,3,5,7	0	0	0	0	99999	0	0	0
Potassium; above normal range; n=1,3,3,3,0,3,5,7	0	1	0	1	99999	0	1	2
Protein; below normal range; n=3,3,4,3,1,4,4,7	0	0	0	0	0	0	1	2
Protein; above normal range; n=3,3,4,3,1,4,4,7	0	0	0	0	0	0	0	1
Sodium; below normal range; n=3,3,4,3,1,4,5,8	1	0	0	0	0	0	0	1
Sodium; above normal range; n=3,3,4,3,1,4,5,8	0	0	0	1	0	0	0	0
Urea; below normal range; n=2,3,4,2,1,4,5,8	0	0	1	0	0	0	0	3
Urea; above normal range; n=2,3,4,2,1,4,5,8	0	0	0	0	0	0	0	0
No statistical analyses for this end point								

Primary: Part B: Number of Subjects With Abnormal Clinical Chemistry Results Anytime Between 40 to 48 Hours Post-dose 10	
End point title	Part B: Number of Subjects With Abnormal Clinical Chemistry Results Anytime Between 40 to 48 Hours Post-dose 10 [37]
End point description	Clinical chemistry parameters included creatinine, urea, AST, ALT, GGT, ALP, LDH, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, and calcium. Institutional laboratory normal ranges were used. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5

Notes
[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	0 [38]	4	5	8
Units: Subjects								
ALT; below normal range; n=3,3,3,2,0,3,5,6	0	0	0	0		0	0	0
ALT; above normal range; n=3,3,3,2,0,3,5,6	0	0	0	0		0	0	1

Albumin; below normal range; n=3,3,4,2,0,4,4,6	0	0	0	0		0	0	1
Albumin; above normal range; n=3,3,4,2,0,4,4,6	0	0	0	0		0	0	1
ALP; below normal range; n=3,3,3,2,0,4,4,7	0	0	0	0		0	0	0
ALP; above normal range; n=3,3,3,2,0,4,4,7	0	0	1	0		0	0	0
AST; below normal range; n=3,3,2,2,0,2,4,7	0	0	0	0		0	0	0
AST; above normal range; n=3,3,2,2,0,2,4,7	0	0	0	0		0	0	0
Bilirubin; below normal range; n=3,3,4,2,0,4,4,6	1	0	1	0		0	0	1
Bilirubin; above normal range; n=3,3,4,2,0,4,4,6	0	0	0	0		0	0	0
Calcium; below normal range; n=3,3,3,2,0,4,4,7	0	0	0	0		0	0	0
Calcium; above normal range; n=3,3,3,2,0,4,4,7	0	1	1	0		1	0	5
Chloride; below normal range; n=3,3,4,2,0,4,5,8	1	0	0	0		0	0	0
Chloride; above normal range; n=3,3,4,2,0,4,5,8	0	0	0	0		0	0	0
Creatinine; below normal range; n=2,3,4,2,0,4,5,8	1	0	0	1		0	1	4
Creatinine; above normal range; n=2,3,4,2,0,4,5,8	0	0	0	0		0	0	0
GGT; below normal range; n=3,3,4,2,0,4,4,7	0	0	0	0		0	0	0
GGT; above normal range; n=3,3,4,2,0,4,4,7	0	0	0	1		0	1	0

Glucose; below normal range; n=2,3,4,2,0,4,5,8	0	0	0	0		0	0	0
Glucose; above normal range; n=2,3,4,2,0,4,5,8	0	0	0	0		0	1	1
LDH; below normal range; n=2,3,2,1,0,2,3,6	0	0	0	0		0	0	0
LDH; above normal range; n=2,3,2,1,0,2,3,6	0	0	0	0		0	0	1
Potassium; below normal range; n=2,3,2,2,0,2,4,6	0	0	0	0		0	0	0
Potassium; above normal range; n=2,3,2,2,0,2,4,6	0	1	0	1		0	1	1
Protein; below normal range; n=3,3,4,2,0,4,4,7	0	0	0	0		0	1	1
Protein; above normal range; n=3,3,4,2,0,4,4,7	0	0	0	0		0	0	0
Sodium; below normal range; n=3,3,4,2,0,4,5,8	0	0	0	0		0	0	0
Sodium; above normal range; n=3,3,4,2,0,4,5,8	0	0	0	1		0	0	0
Urea; below normal range; n=3,3,4,2,0,4,5,8	1	0	1	1		0	1	0
Urea; above normal range; n=3,3,4,2,0,4,5,8	0	0	0	0		0	0	0

Notes
[38] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Urinalysis Results at Baseline	
End point title	Part A: Number of Subjects With Abnormal Urinalysis Results at Baseline [39]
End point description	Following urine parameters were analysed: epithelial cells (normal range: 0 to 5 cells per high power field [hpf]), erythrocytes (0 to 2 per hpf), granular casts (0 per low power field [lpf]), hyaline casts (0 to 1 per lpf), leukocytes (0 to 5 per hpf), RBC casts (0 per lpf), WBC casts (0 per lpf), waxy casts (0 per lpf) and pH (5 to 8). Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)
Notes [39] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	2	7	3	6
Units: Subjects				
Epithelial Cells; below normal range; n=2,7,3,6	0	0	0	0
Epithelial Cells; above normal range; n=2,7,3,6	0	0	0	0
Erythrocytes; below normal range; n=2,7,3,6	0	0	0	0

Erythrocytes; above normal range; n=2,7,3,6	0	0	0	0
Granular casts; below normal range; n=2,7,3,6	0	0	0	0
Granular casts; above normal range; n=2,7,3,6	0	0	0	0
Hyaline casts; below normal range; n=2,7,3,6	0	0	0	0
Hyaline casts; above normal range; n=2,7,3,6	0	0	0	0
Leukocytes; below normal range; n=2,7,3,6	0	0	0	0
Leukocytes; above normal range; n=2,7,3,6	0	0	0	0
RBC cast; below normal range; n=2,7,3,6	0	0	0	0
RBC cast; above normal range; n=2,7,3,6	0	0	0	0
WBC cast; below normal range; n=2,7,3,6	0	0	0	0
WBC cast; above normal range; n=2,7,3,6	0	0	0	0
Waxy cast; below normal range; n=2,7,3,6	0	0	0	0
Waxy cast; above normal range; n=2,7,3,6	0	0	0	0
pH; below normal range; n=2,7,3,4	0	0	0	0
pH; above normal range; n=2,7,3,4	0	1	0	0
No statistical analyses for this end point				

Primary: Part A: Number of Subjects With Abnormal Urinalysis Results at 48 Hours Post-dose	
End point title	Part A: Number of Subjects With Abnormal Urinalysis Results at 48 Hours Post-dose [40]
End point description	Following urine parameters were analysed: epithelial cells (normal range: 0 to 5 cells per hpf), erythrocytes (0 to 2 per hpf), granular casts (0 per lpf), hyaline casts (0 to 1 per lpf), leukocytes (0 to 5 per hpf), RBC casts (0 per lpf), WBC casts (0 per lpf), waxy casts (0 per lpf) and pH (5 to 8). Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	48 hours post-dose on Day 1
Notes [40] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive analysis was planned.	

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	0 [41]	6
Units: Subjects				
Epithelial Cells; below normal range; n=3,6,0,6	0	0		0
Epithelial Cells; above normal range; n= 3,6,0,6	0	0		0

Erythrocytes; below normal range; n=3,6,0,6	0	0		0
Erythrocytes; above normal range; n=3,6,0,6	1	0		1
Granular casts; below normal range; n=3,6,0,6	0	0		0
Granular casts; above normal range; n=3,6,0,6	0	0		0
Hyaline casts; below normal range; n=3,6,0,6	0	0		0
Hyaline casts; above normal range; n=3,6,0,6	0	0		0
Leukocytes; below normal range; n=3,6,0,6	0	0		0
Leukocytes; above normal range; n=3,6,0,6	0	0		0
RBC cast; below normal range; n=3,6,0,6	0	0		0
RBC cast; above normal range; n=3,6,0,6	0	0		0
WBC cast; below normal range; n=3,6,0,6	0	0		0
WBC cast; above normal range; n=3,6,0,6	0	0		0
Waxy cast; below normal range; n=3,6,0,6	0	0		0
Waxy cast; above normal range; n=3,6,0,6	0	0		0
pH; below normal range; n=2,6,0,5	0	0		0
pH; above normal range; n=2,6,0,5	0	2		1

Notes [41] - No subjects were evaluable	
No statistical analyses for this end point	
Primary: Part B: Number of Subjects With Abnormal Urinalysis Results at Baseline	
End point title	Part B: Number of Subjects With Abnormal Urinalysis Results at Baseline [42]
End point description	Following urine parameters were analysed: epithelial cells (normal range: 0 to 5 cells per hpf), erythrocytes (0 to 2 per hpf), granular casts (0 per lpf), hyaline casts (0 to 1 per lpf), leukocytes (0 to 5 per hpf), RBC casts (0 per lpf), WBC casts (0 per lpf), waxy casts (0 per lpf) and pH (5 to 8). Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)
Notes [42] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.	

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	2	3	2	2	1	2	4	5
Units: Subjects								

Epi Cells; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Epi Cells; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Ery; below normal range; n=2,3,2,2,1,2,4,3	0	0	0	0	0	0	0	1
Ery; above normal range; n=2,3,2,2,1,2,4,3	0	1	1	0	0	0	0	0
Gran casts; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Gran casts; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Hya casts; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Hya casts; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Leuko; below normal range; n=2,3,2,2,1,2,4,3	0	0	0	0	0	0	0	1
Leuko; above normal range; n=2,3,2,2,1,2,4,3	0	0	0	0	0	1	2	1
RBC cast; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
RBC cast; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
WBC cast; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
WBC cast; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Waxy cast; below normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0
Waxy cast; above normal range; n=2,3,1,2,1,2,2,2	0	0	0	0	0	0	0	0

pH; below normal range; n=3,3,2,3,1,2,4,5	0	0	0	0	0	0	0	0
pH; above normal range; n=3,3,2,3,1,2,4,5	0	0	1	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Urinalysis Results Anytime Between 40 to 48 Hours Post-Dose 10

End point title	Part B: Number of Subjects With Abnormal Urinalysis Results Anytime Between 40 to 48 Hours Post-Dose 10 [43]
End point description	Following urine parameters were analysed: epithelial cells (normal range: 0 to 5 cells per hpf), erythrocytes (0 to 2 per hpf), granular casts (0 per lpf), hyaline casts (0 to 1 per lpf), leukocytes (0 to 5 per hpf), RBC casts (0 per lpf), WBC casts (0 per lpf), waxy casts (0 per lpf) and pH (5 to 8). Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5

Notes
[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	2	3	2	1	0 [44]	0 [45]	3	5
Units: Subjects								
Epi Cells; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Epi Cells; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Ery; below normal range; n=2,3,2,1,0,0,3,2	0	0	0	0			0	0
Ery; above normal range; n=2,3,2,1,0,0,3,2	0	0	1	0			2	0
Gran casts; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Gran casts; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Hya casts; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Hya casts; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Leuko; below normal range; n=2,3,2,1,0,0,3,2	0	0	0	0			0	0
Leuko; above normal range; n=2,3,2,1,0,0,3,2	0	0	0	0			1	0
RBC cast; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
RBC cast; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0

WBC cast; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
WBC cast; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Waxy cast; below normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
Waxy cast; above normal range; n=2,3,1,1,0,0,1,2	0	0	0	0			0	0
pH; below normal range; n=2,3,2,1,0,0,3,5	0	0	0	0			0	0
pH; above normal range; n=2,3,2,1,0,0,3,5	1	0	1	1			0	2

Notes
[44] - No subjects were evaluable
[45] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Baseline

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Baseline [46]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QT interval corrected by Bazzett's formula (QTcB) interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[46] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose [47]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose on Day 1

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

end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Subjects	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 18 to 24 Hours Post-dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 18 to 24 Hours Post-dose [48]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 18 to 24 hours post-dose on Day 1

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

end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Baseline

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Baseline [49]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP.
End point type	Primary
End point timeframe	Baseline (pre-dose on Day 1)

Notes
[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	3	1	4	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at 48 Hours Post-dose

End point title	Part A: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at 48 Hours Post-dose [50]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	48 hours post-dose on Day 1

Notes
[50] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis was planned.

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	6	2	6
Units: Subjects	0	1	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 1

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 1 [51]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose 1 on Day 1

Notes
[51] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	3	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 3

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 3 [52]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 3 (Day 2)

Notes
[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 5

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 5 [53]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 5 (Day 3)

Notes
[53] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 6

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 4 to 5 Hours Post-Dose 6 [54]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 4 to 5 hours post-dose 6 (Day 3)

Notes
[54] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	3	2	1	4	4	7
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 10

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 10 [55]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose (Day 5)

Notes
[55] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	2	1	0 [56]	0 [57]	3	3	4
Units: Subjects	0	0	0			0	0	0

Notes
[56] - No subjects were evaluable
[57] - No subjects were evaluable

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 8

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation at Pre-dose 8 [58]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Pre-dose 8 (Day 4)

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

end point.
Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	2	2	2	1	1	4	5
Units: Subjects	0	0	0	0	0	0	0	0

No statistical analyses for this end point

Primary: Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 40 to 48 Hours Post-Dose 10

End point title	Part B: Number of Subjects With Abnormal Clinically Significant Electrocardiogram (ECG) Results per Investigator's Interpretation Anytime Between 40 to 48 Hours Post-Dose 10 [59]
End point description	A 12-lead ECG was performed for assessment of following ECG parameters: ventricular heart rate, PR interval, QRS interval, QT interval and QTcB interval. Number of subjects with abnormal clinically significant results for any ECG parameter per investigators interpretation are reported in this outcome measure. Safety population included all subjects who received at least 1 dose of IMP. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Primary
End point timeframe	Anytime between 40 to 48 hours post-dose 10 on Day 5

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

end point. Justification: The endpoint is specific to Part B; hence, only arms for Part B are included.								
End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	0 [60]	4	5	8
Units: Subjects	0	0	0	0		0	0	0
Notes [60] - No subjects were evaluable								
No statistical analyses for this end point								

Secondary: Part A: Time to Maximum Plasma Concentration (tmax)	
End point title	Part A: Time to Maximum Plasma Concentration (tmax)
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement.
End point type	Secondary
End point timeframe	Anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Hours				
median (full range (min-max))	4.17 (4 to 4.5)	4.58 (4.42 to 6.18)	7 (4.87 to 48.3)	4.78 (2 to 6.67)

No statistical analyses for this end point

Secondary: Part B: Time to Maximum Plasma Concentration (tmax)

End point title	Part B: Time to Maximum Plasma Concentration (tmax)
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'n' signifies number of subjects evaluable for the specified categories.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	4	3	4	8
Units: Hours					

median (full range (min-max))					
Dose 1; n=3,4,3,4,8	4.6 (4.33 to 4.63)	4.32 (3.58 to 11.6)	4.17 (2.5 to 4.17)	4.03 (3.77 to 5.5)	4.31 (4.08 to 12)
Dose 6; n=3,3,2,3,8	4.43 (4.38 to 4.5)	3.95 (3.67 to 4.88)	4.53 (4.05 to 5)	4.58 (3.58 to 11.5)	4.29 (0 to 11.8)

No statistical analyses for this end point

Secondary: Part A: Maximum Observed Plasma Concentration (Cmax)

End point title	Part A: Maximum Observed Plasma Concentration (Cmax)
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement.
End point type	Secondary
End point timeframe	Anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	3	6
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)	1.59 ± 2.76	8.08 ± 7.94	2.98 ± 3.09	28 ± 17.5

No statistical analyses for this end point

Secondary: Part B: Maximum Observed Plasma Concentration (Cmax)					
End point title	Part B: Maximum Observed Plasma Concentration (Cmax)				
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'n' signifies number of subjects evaluable for the specified categories.				
End point type	Secondary				
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)				
End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	4	3	4	8
Units: Nanogram per milliliter					
arithmetic mean (standard deviation)					
Dose 1; n=3,4,3,4,8	43.2 ± 36.7	24.9 ± 20	115 ± 182	39.3 ± 26.4	56.5 ± 88.1
Dose 6; n=3,3,2,3,8	30.9 ± 31.3	67.8 ± 86.3	212 ± 157	133 ± 64.8	177 ± 151
No statistical analyses for this end point					

Secondary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero to 12 Hours (AUC0-12)	
End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero to 12 Hours (AUC0-12)

End point description	AUC(0 to 12) was calculated using the linear trapezoidal method. No sampling was done at 0 hour. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	0 hour, anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	3	7	2	6
Units: Hours*nanogram per milliliter				
arithmetic mean (standard deviation)	9.22 ± 16	45 ± 48	6.46 ± 9.14	201 ± 143

No statistical analyses for this end point

Secondary: Part B: Area Under the Plasma Concentration Time Curve From Time Zero to 12 Hours (AUC0-12)

End point title	Part B: Area Under the Plasma Concentration Time Curve From Time Zero to 12 Hours (AUC0-12)
End point description	AUC(0 to 12) was calculated using the linear trapezoidal method. No sampling was done at 0 hour on Day 1. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies number of subjects evaluable for the specified categories. 99999 indicates data could not be calculated due to insufficient number of subjects.

End point type	Secondary
End point timeframe	Day 1 Dose 1 (0 hour, anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	1	2	1	4
Units: Hours*nanogram per milliliter					
arithmetic mean (standard deviation)					
Dose 1; n=0,0,2,1,4	99999 ± 99999	99999 ± 99999	1170 ± 1460	127 ± 99999	160 ± 120
Dose 6; 1,1,0,1,1	87.9 ± 99999	184 ± 99999	99999 ± 99999	1110 ± 99999	1600 ± 99999

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Measurable Concentration (AUC[0 to t])

End point title	Part A: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Measurable Concentration (AUC[0 to t])
End point description	Area under the plasma concentration-time curve from time 0 to the last measurable concentration was determined using the linear trapezoidal method. No sampling was done at 0 hour. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects

	Analysed' signifies number of subjects evaluable for this endpoint. 99999 signifies data could not be calculated due to insufficient subjects.
End point type	Secondary
End point timeframe	0 hour, anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	1	6	2	6
Units: Hours*nanogram per milliliter				
arithmetic mean (standard deviation)	23.1 ± 99999	48.1 ± 49.9	14 ± 1.46	287 ± 217

No statistical analyses for this end point

Secondary: Part B: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Measurable Concentration (AUC[0 to t])

End point title	Part B: Area Under the Plasma Concentration-Time Curve From Time 0 to the Last Measurable Concentration (AUC[0 to t])
End point description	Area under the plasma concentration-time curve from time 0 to the last measurable concentration was determined using the linear trapezoidal method. No sampling was done at 0 hour on Day 1. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary

End point timeframe	Day 1 Dose 1 (0 hour, anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	4	2	4	8
Units: Hours*nanogram per milliliter					
arithmetic mean (standard deviation)					
Dose 1; n=3,4,2,4,8	288 ± 251	163 ± 132	1170 ± 1460	342 ± 240	315 ± 386
Dose 6; n=3,3,2,3,8	225 ± 233	477 ± 594	1560 ± 1010	1310 ± 802	1140 ± 845

No statistical analyses for this end point

Secondary: Part B: Terminal Half-life (t1/2)

End point title	Part B: Terminal Half-life (t1/2)
End point description	T1/2 was calculated as loge (2) divided by kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [61]	0 [62]	0 [63]	0 [64]	0 [65]
Units: Hours					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[61] - No subjects were evaluable
[62] - No subjects were evaluable
[63] - No subjects were evaluable
[64] - No subjects were evaluable
[65] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part A: Terminal Half-life (t1/2)

End point title	Part A: Terminal Half-life (t1/2)
End point description	T1/2 was calculated as loge (2) divided by kel, where kel is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	0 [66]	0 [67]	0 [68]	5
Units: Hours				
arithmetic mean (standard deviation)	±	±	±	6.22 ± 1.46

Notes
[66] - No subjects were evaluable
[67] - No subjects were evaluable
[68] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0 to inf)

End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0 to inf)
End point description	AUCinf was determined as AUC(0 to t) + (Clast/kel), where Clast was the plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis and kel was the terminal phase rate. No sampling was done at 0 hour. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	0 hour, anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	0 [69]	0 [70]	0 [71]	5
Units: Hours*nanogram per milliliter				
arithmetic mean (standard deviation)	±	±	±	231 ± 161

Notes
[69] - No subjects were evaluable
[70] - No subjects were evaluable
[71] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0 to inf)

End point title	Part B: Area Under the Plasma Concentration Time Curve From Time Zero to Infinity (AUC0 to inf)
End point description	AUCinf was determined as AUC(0 to t) + (Clast/kel), where Clast was the plasma concentration at the last quantifiable timepoint estimated from the log-linear regression analysis and kel was the terminal phase rate. No sampling was done at 0 hour on Day 1. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary

End point timeframe	Day 1 Dose 1 (0 hour, anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [72]	0 [73]	0 [74]	0 [75]	0 [76]
Units: Hours*nanogram per milliliter					
geometric mean (geometric coefficient of variation)	±	±	±	±	±

Notes
[72] - No subjects were evaluable
[73] - No subjects were evaluable
[74] - No subjects were evaluable
[75] - No subjects were evaluable
[76] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part A: Trough Concentration at the end of First Dosing Interval (C12)

End point title	Part A: Trough Concentration at the end of First Dosing Interval (C12)
End point description	PK Population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	At 12 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	0 [77]	0 [78]	0 [79]	0 [80]
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)	±	±	±	±

Notes
[77] - No subjects were evaluable
[78] - No subjects were evaluable
[79] - No subjects were evaluable
[80] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Trough Concentration at the end of First Dosing Interval (C12)

End point title	Part B: Trough Concentration at the end of First Dosing Interval (C12)
End point description	PK Population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	At 12 hours post-dose 6

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	2	3	8
Units: Nanograms per milliliter					
arithmetic mean (standard deviation)	7.6 ± 8.33	9.55 ± 9.75	36.9 ± 5.3	89.8 ± 99.1	124 ± 167

No statistical analyses for this end point

Secondary: Part A: Predicted Plasma Clearance

End point title	Part A: Predicted Plasma Clearance
End point description	Clearance was calculated as Dose divided by AUC(0 to inf). PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	0 [81]	0 [82]	0 [83]	5
Units: Liters per hour per kilogram				
arithmetic mean (standard deviation)	±	±	±	12.7 ± 7.66

Notes
[81] - No subjects were evaluable
[82] - No subjects were evaluable
[83] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Predicted Plasma Clearance

End point title	Part B: Predicted Plasma Clearance
End point description	Clearance was calculated as Dose divided by AUC(0 to inf). PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [84]	0 [85]	0 [86]	0 [87]	0 [88]
Units: Liters per hour per kilogram					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[84] - No subjects were evaluable
[85] - No subjects were evaluable
[86] - No subjects were evaluable
[87] - No subjects were evaluable
[88] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part A: Apparent Volume of Distribution of the Drug After Extravascular Administration

End point title	Part A: Apparent Volume of Distribution of the Drug After Extravascular Administration
End point description	Apparent volume of distribution was estimated as Dose/Kel*AUC(0 to inf), where Kel=apparent first-order terminal elimination rate constant. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Anytime between 4 to 5 hours, anytime between 6 to 8 hours, 12 hours, 18 to 24 hours and 48 hours post-dose on Day 1

End point values	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg
Number of subjects analysed	0 [89]	0 [90]	0 [91]	5
Units: Litres per kilogram				
arithmetic mean (standard deviation)	±	±	±	119 ± 87.4

Notes
[89] - No subjects were evaluable
[90] - No subjects were evaluable
[91] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Apparent Volume of Distribution of the Drug After Extravascular Administration

End point title	Part B: Apparent Volume of Distribution of the Drug After Extravascular Administration
End point description	Apparent volume of distribution was estimated as Dose/Kel*AUC(0 to inf), where Kel=apparent first-order terminal elimination rate constant. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [92]	0 [93]	0 [94]	0 [95]	0 [96]
Units: Liters per kilogram					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[92] - No subjects were evaluable
[93] - No subjects were evaluable
[94] - No subjects were evaluable
[95] - No subjects were evaluable
[96] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Accumulation Ratio

End point title	Part B: Accumulation Ratio
End point description	Accumulation ratio was calculated as ratio of the area under the curve (AUC) during a single dosing interval under steady state conditions to the AUC during a dosing interval after one singe dose. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [97]	0 [98]	0 [99]	0 [100]	0 [101]
Units: Ratio					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[97] - No subjects were evaluable
[98] - No subjects were evaluable
[99] - No subjects were evaluable
[100] - No subjects were evaluable
[101] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Percentage Fluctuation

End point title	Part B: Percentage Fluctuation
End point description	Percentage fluctuation was calculated as 100*(Cmax-Cmin)/Cavg, where Cmin=minimum plasma concentration and Cmax measured over dosing interval. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint. 99999 indicates data could not be calculated due to insufficient number of subjects.
End point type	Secondary
End point timeframe	Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	1	0 [102]	1	1
Units: Percentage of fluctuation					
arithmetic mean (standard deviation)	132 ± 99999	123 ± 99999	±	8.63 ± 99999	98.1 ± 99999

Notes
[102] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Area Under the Plasma Concentration Time Curve From Time Zero to the end of Last Dosing Interval (AUC0-tau)

End point title	Part B: Area Under the Plasma Concentration Time Curve From Time Zero to the end of Last Dosing Interval (AUC0-tau)
End point description	AUC(0 to tau) was determined using the linear trapezoidal method. No sampling was done at 0 hour. PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint. 99999 indicates data could not be calculated due to insufficient number of subjects.
End point type	Secondary
End point timeframe	Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	1	0 [103]	1	1
Units: Hours*nanogram per milliliter					
arithmetic mean (standard deviation)	87.9 ± 99999	184 ± 99999	±	1110 ± 99999	1600 ± 99999

Notes
[103] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Average Plasma Concentration Over Dosing Interval (Cavg)	
End point title	Part B: Average Plasma Concentration Over Dosing Interval (Cavg)
End point description	Cavg was estimated as AUC(0 to tau)/tau, where tau=dosing interval (12 hours). PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint. 99999 indicates data could not be calculated due to insufficient number of subjects.
End point type	Secondary
End point timeframe	Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	1	1	0 [104]	1	1
Units: Nanogram per milliliter					
arithmetic mean (standard deviation)	7.32 ± 99999	15.3 ± 99999	±	92.7 ± 99999	133 ± 99999

Notes
[104] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Minimum Observed Plasma Concentration

End point title	Part B: Minimum Observed Plasma Concentration
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg

Number of subjects analysed	0 [105]	0 [106]	0 [107]	0 [108]	0 [109]
Units: Nanograms per milliliter					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[105] - No subjects were evaluable
[106] - No subjects were evaluable
[107] - No subjects were evaluable
[108] - No subjects were evaluable
[109] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Plasma Trough Concentration

End point title	Part B: Plasma Trough Concentration
End point description	PK population included all subjects who received IMP and had at least 1 post-dose PK concentration measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Day 1 Dose 1 (anytime between 4 to 5 hours post-dose, 12 hours post-dose), Day 3 Dose 6 (pre-dose, anytime between 4 to 5 hours post-dose, 12 hours post-dose)

End point values	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: RV521 2.5 mg/kg	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	0 [110]	0 [111]	0 [112]	0 [113]	0 [114]

Units: Nanograms per milliliter					
arithmetic mean (standard deviation)	±	±	±	±	±

Notes
[110] - No subjects were evaluable
[111] - No subjects were evaluable
[112] - No subjects were evaluable
[113] - No subjects were evaluable
[114] - No subjects were evaluable

No statistical analyses for this end point

Secondary: Part B: Percent Change From Baseline in Logarithm to Base10 (Log10) Total RSV Viral Load by Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR)

End point title	Part B: Percent Change From Baseline in Logarithm to Base10 (Log10) Total RSV Viral Load by Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR)
End point description	Percent change from baseline in log10 total RSV viral load was analysed using a mixed effects analysis of covariance (ANCOVA) model. The model was fitted to the subjects treated at the final doses selected for Cohort 5 as pre-planned in statistical analysis plan. Modified Intent to Treat (mITT) population included all subjects who received at least 1 dose of IMP (RV521 or placebo) and had a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during blind data review meeting. Here, 'n' signifies subjects evaluable at the specified timepoints.
End point type	Secondary
End point timeframe	Baseline (pre-dose on Day 1), 60 hours and 156 hours after first dose on Day 1

End point values	Cohort 4 and 5 combined: RV521 2.5 mg/kg	Cohort 4 and 5 combined: Placebo
Number of subjects analysed	12	6
Units: Percent change		
least squares mean (standard error)		
60 hours; n=5,11	-31.29 ± 8.19	-23.27 ± 10.48
156 hours; n=4,12	-47.53 ± 8.03	-32.31 ± 11.52

Statistical analysis title	Placebo versus RV521 2.5 mg/kg
Statistical analysis description	Analysis was performed using mixed effects analysis of covariance model on change from baseline in viral load, including a random effect for subject and fixed effects for treatment group, baseline human rhinovirus/enterovirus status (present or absent), visit, vist by treatment group interaction, and baseline viral load as a covariate.
Comparison groups	Cohort 4 and 5 combined: Placebo v Cohort 4 and 5 combined: RV521 2.5 mg/kg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other [115]
Method	
Parameter type	Mean difference (net)

Point estimate	-15.22
Confidence interval	
level	95%
sides	2-sided
lower limit	-40.15
upper limit	9.7
Notes [115] - 156 hours	
Statistical analysis title	Placebo versus RV521 2.5 mg/kg
Statistical analysis description	Analysis was performed using mixed effects analysis of covariance model on change from baseline in viral load, including a random effect for subject and fixed effects for treatment group, baseline human rhinovirus/enterovirus status (present or absent), visit, vist by treatment group interaction, and baseline viral load as a covariate.
Comparison groups	Cohort 4 and 5 combined: Placebo v Cohort 4 and 5 combined: RV521 2.5 mg/kg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other [116]
Method	
Parameter type	Mean difference (net)

Point estimate	-8.02
Confidence interval	
level	95%
sides	2-sided
lower limit	-31.78
upper limit	15.74
Notes [116] - 60 hours	

Secondary: Part B: Percent Change From Baseline in Logarithm to Base10 (Log10) Total RSV Viral Load by Cell-Based Infectivity Assay (CBIA)	
End point title	Part B: Percent Change From Baseline in Logarithm to Base10 (Log10) Total RSV Viral Load by Cell-Based Infectivity Assay (CBIA)
End point description	Percent change from baseline in log10 total RSV viral load was analysed using a mixed effects ANCOVA model. The model was fitted to the subjects treated at the final doses selected for Cohort 5 as pre-planned in statistical analysis plan. mITT population included all subjects who received at least 1 dose of IMP (RV521 or placebo) and had a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during blind data review meeting. Here, 'n' signifies subjects evaluable at the specified timepoints.
End point type	Secondary
End point timeframe	Baseline (pre-dose on Day 1), 60 hours and 156 hours after first dose on Day 1

End point values	Cohort 4 and 5 combined: RV521 2.5 mg/kg	Cohort 4 and 5 combined: Placebo
Number of subjects analysed	12	6
Units: Percent change		
least squares mean (standard error)		
60 hours; 5, 11	-54.74 ± 34.87	-69.56 ± 46.32
156 hours; 4, 12	-41.20 ± 34.01	-10.00 ± 51.88

Statistical analysis title	Placebo versus RV521 2.5 mg/kg
Statistical analysis description	Analysis was performed using mixed effects analysis of covariance model on change from baseline in viral load, including a random effect for subject and fixed effects for treatment group, baseline human rhinovirus/enterovirus status (present or absent), visit, vist by treatment group interaction, and baseline viral load as a covariate.
Comparison groups	Cohort 4 and 5 combined: Placebo v Cohort 4 and 5 combined: RV521 2.5 mg/kg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other [117]
Method	
Parameter type	Mean difference (net)

Point estimate	-31.19
Confidence interval	
Level	95%
sides	2-sided
lower limit	-143.96
upper limit	81.57
Notes [117] - 156 hours	
Statistical analysis title	Placebo versus RV521 2.5 mg/kg
Statistical analysis description	Analysis was performed using mixed effects analysis of covariance model on change from baseline in viral load, including a random effect for subject and fixed effects for treatment group, baseline human rhinovirus/enterovirus status (present or absent), visit, vist by treatment group interaction, and baseline viral load as a covariate.
Comparison groups	Cohort 4 and 5 combined: Placebo v Cohort 4 and 5 combined: RV521 2.5 mg/kg
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other [118]
Method	
Parameter type	Mean difference (net)

Point estimate	14.82
Confidence interval	
Level	95%
Sides	2-sided
lower limit	-91.68
upper limit	121.33
Notes [118] - 60 hours	

Secondary: Part B: Time to Resolution of RSV-Related Signs and Symptoms	
End point title	Part B: Time to Resolution of RSV-Related Signs and Symptoms
End point description	Time to resolution was calculated for RSV-related signs and symptoms that were present at study start and was defined as the time of randomisation to the time that RSV-related signs and symptoms were absent. mITT population included all subjects who received at least 1 dose of IMP (RV521 or placebo) and had a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during blind data review meeting. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Up to 13 days

End point values	Cohort 3: Placebo	Cohort 3: RSV1 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 5: RV521 2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Days								
median (full range (min-max))	6.20 (6.1 to 6.6)	6.20 (6.2 to 6.3)	6.45 (5.9 to 6.8)	3.80 (2.6 to 5.0)	4.90 (4.9 to 4.9)	6.30 (4.6 to 6.9)	6.00 (2.5 to 6.7)	6.10 (4.1 to 6.9)
No statistical analyses for this end point								

Secondary: Part B: Time to Improvement in RSV-Related Signs and Symptoms	
End point title	Part B: Time to Improvement in RSV-Related Signs and Symptoms
End point description	Time to improvement was calculated for RSV-related signs and symptoms that were classified as moderate or severe during the course of the study and was defined as the time from randomisation to the time that RSV-related signs and symptoms were mild or absent. mITT population included all subjects who received at least 1 dose of IMP (RV521 or placebo) and had a pre-treatment positive RSV nasopharyngeal swab confirmed by the central laboratory and agreed by the project team during blind data review meeting. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.
End point type	Secondary
End point timeframe	Up to 13 days

End point values	Cohort 3: Placebo	Cohort 3: RSV1	Cohort 3: RV521	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521	Cohort 5: Placebo	Cohort 5: RV521

		2.5 mg/kg	3.5 mg/kg			2.5 mg/kg		2.5 mg/kg
Number of subjects analysed	2	3	4	2	1	4	5	8
Units: Days								
median (full range (min-max))	2.25 (1.5 to 3.0)	0.50 (0.5 to 6.3)	3.15 (2.1 to 5.9)	2.55 (1.1 to 4.0)	1.90 (1.9 to 1.9)	4.35 (3.6 to 6.9)	3.00 (1.0 to 6.0)	6.00 (1.5 to 6.9)
No statistical analyses for this end point								

Secondary: Part B: RSV Clinical Scoring System Scores	
End point title	Part B: RSV Clinical Scoring System Scores
End point description	RSV clinical score was a composite score for infants with RSV infection >= 1 month of age based on 4 items (respiratory rate, wheezing, retraction of respiratory muscles and general condition). Score for each item ranged from 0 to 3 where 0=none/normal and 3=severe. Total score was calculated as sum of individual items and ranged from 0 to 12, where higher score indicated severe disease. RSV symptoms were graded as mild: score <=5, moderate: score > 5 but < 9 and severe: score >=9. mITT population was analysed. Here, 'Number of Subjects Analysed' signifies subjects evaluable for this endpoint and 'n' signifies subjects evaluable at the specified timepoints. 99999 signifies data could not be calculated due to insufficient subjects.
End point type	Secondary
End point timeframe	Baseline (pre-dose 1 on Day 1), pre-dose 3, pre-dose 5, pre-dose 7, pre-dose 9, anytime between 40 to 48 hours post-dose 10 on Day 5

End point values	Cohort 3: Placebo	Cohort 3: RSV1	Cohort 3: RV521	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521	Cohort 5: Placebo	Cohort 5: RV521

		2.5 mg/kg	3.5 mg/kg			2.5 mg/kg		2.5 mg/kg
Number of subjects analysed	3	3	4	2	1	4	5	8
Units: Units on a scale								
arithmetic mean (standard deviation)								
Baseline; n=2,3,4,2,1,4,5,8	3.5 ± 2.12	5.0 ± 1.73	6.8 ± 2.50	4.5 ± 6.36	8.0 ± 99999	6.8 ± 2.22	6.2 ± 3.56	6.0 ± 2.73
pre-dose 3; n=3,3,4,2,1,4,5,8	2.0 ± 1.73	4.0 ± 2.65	2.5 ± 1.29	1.0 ± 1.41	4.0 ± 99999	5.0 ± 0.00	1.8 ± 1.10	4.3 ± 2.38
pre-dose 5; n=3,3,4,2,1,4,5,8	1.0 ± 1.00	2.7 ± 2.08	1.8 ± 1.50	2.5 ± 3.54	3.0 ± 99999	3.3 ± 0.96	1.4 ± 1.14	3.9 ± 2.75
pre-dose 7; n=3,3,4,2,1,3,5,8	0.7 ± 0.58	3.0 ± 1.73	1.3 ± 1.50	2.5 ± 3.54	1.0 ± 99999	1.3 ± 0.58	1.6 ± 0.55	2.3 ± 2.12
pre-dose 9; n=1,2,2,1,1,2,4,4	0.0 ± 99999	3.5 ± 2.12	1.5 ± 0.71	1.0 ± 99999	1.0 ± 99999	2.0 ± 1.41	1.8 ± 0.50	2.3 ± 0.96
40 to 48 hours post-dose 10; n=3,3,4,2,0,3,5,8	0.3 ± 0.58	1.0 ± 1.00	0.5 ± 0.58	0.0 ± 0.00	99999 ± 99999	1.0 ± 1.00	1.2 ± 1.10	0.6 ± 0.52
No statistical analyses for this end point								

Adverse events	
Adverse events information	
Timeframe for reporting adverse events	From start of IMP on Day 1 up to Day 7 for Part A; From start of IMP on Day 1 up to Day 12 for Part B
Adverse event reporting additional description	Same event may appear as SAE and non-SAE, what is presented are distinct events. Event may be categorised as serious in 1 subject and as non-serious in another or 1 subject may have experienced both serious and non-serious event during study.
Assessment type	Non-systematic
Dictionary used for adverse event reporting	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	Cohort 1: RV521 1.0 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 1.0 milligram per kilogram (mg/kg) of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.0 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.0 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 1: RV521 2.5 mg/kg

Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received a single dose of 2.5 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 2: RV521 2.0 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received a single dose of 2 mg/kg of RV521 orally on Day 1.
Reporting group title	Cohort 3: Placebo
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 5: RV521 2.5 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 3: RV521 3.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 3.5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 3: RV521 5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 4: Placebo

Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 4: RV521 2.5 mg/kg
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 5: Placebo
Reporting group description	Infants aged >=1 month to <6 months hospitalised with RSV LRTI received placebo every 12 hours (BID) orally for 5 days.
Reporting group title	Cohort 3: RSV1 2.5 mg/kg
Reporting group description	Infants aged >=6 months to <=36 months hospitalised with RSV LRTI received RV521 2.5 mg/kg every 12 hours (BID) orally for 5 days.

Serious adverse events	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg	Cohort 3: Placebo	Cohort 5: RV521 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 3: RSV1 2.5 mg/kg
Total subjects affected by serious adverse events												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)

number of deaths (all causes)	0	0	0	0	0	0	0	0	0	0	0	0
number of deaths resulting from adverse events	0	0	0	0	0		0	0				0
General disorders and administration site conditions												
Pyrexia												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Frequency threshold for reporting non-serious adverse events: 0%												

Non-serious adverse events	Cohort 1: RV521 1.0 mg/kg	Cohort 1: RV521 2.0 mg/kg	Cohort 1: RV521 2.5 mg/kg	Cohort 2: RV521 2.0 mg/kg	Cohort 3: Placebo	Cohort 5: RV521 2.5 mg/kg	Cohort 3: RV521 3.5 mg/kg	Cohort 3: RV521 5 mg/kg	Cohort 4: Placebo	Cohort 4: RV521 2.5 mg/kg	Cohort 5: Placebo	Cohort 3: RSV1 2.5 mg/kg
Total subjects affected by non serious adverse events												
subjects affected / exposed	2 / 3 (66.67%)	4 / 7 (57.14%)	3 / 3 (100.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)	1 / 8 (12.50%)	1 / 4 (25.00%)	1 / 3 (33.33%)	1 / 1 (100.00%)	2 / 4 (50.00%)	3 / 5 (60.00%)	2 / 3 (66.67%)
Vascular disorders												
Phlebitis												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
General disorders and administration site conditions												
Pyrexia												

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	1	0	0	0	1	0	2	0
Withdrawal syndrome												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	2 / 4 (50.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	2	1	0
Catheter site inflammation												
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	1	0	0	0	0	0	0	0	0	0	0	0
Oedema peripheral												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)

occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Respiratory, thoracic and mediastinal disorders												
Increased bronchial secretion												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Cyanosis central												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	1	1	0
Atelectasis												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)

occurrences all number	0	0	0	0	0	0	0	0	0	1	1	0
Psychiatric disorders												
Irritability												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	1	0	0	0	0	0	0	0	0
Investigations												
Bacterial test positive												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	1	0	0
Transaminases increased												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)

occurrences all number	0	0	0	0	0	0	0	0	0	0	0	1
Monocyte count decreased												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	0	1
Blood pressure increased												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	1	0	0	0	0	0
Cardiac disorders												
Sinus arrhythmia												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)

occurrences all number	0	1	0	0	0	0	0	0	0	0	0	0
Bradycardia												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Sinus tachycardia												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Blood and lymphatic system disorders												
Thrombocytosis												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)

occurrences all number	0	1	0	0	0	0	0	0	0	0	0	1
Leukocytosis												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	0	1
Ear and labyrinth disorders												
Otorrhoea												
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	1	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders												
Vomiting												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	3 / 3 (100.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 1 (100.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)	2 / 3 (66.67%)

occurrences all number	0	0	4	0	0	0	0	1	1	1	0	2
Post-tussive vomiting												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	1 / 3 (33.33%)
occurrences all number	0	1	0	0	0	0	0	0	0	0	0	1
Diarrhoea												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	1	0	0	0	0	0	0	1	0	0
Anal erythema												
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	1	0	0	0	0	0	0	0	0	0	0
Abdominal distension												

subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	1	0	0	0
Skin and subcutaneous tissue disorders												
Rash macular												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	1	0	0
Rash												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Renal and urinary disorders												

Oliguria												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	1	0	0	0
Infections and infestations												
Bacterial disease carrier												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	2	0	0
Conjunctivitis												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	1 / 8 (12.50%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	1	0	0	0	0	0	0

Urinary tract infection bacterial												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0
Croup infectious												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	2 / 5 (40.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	2	0
Respiratory tract infection bacterial												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	0	0	0	0	0	0	1	0

Metabolism and nutrition disorders												
Hypernatraemia												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	1	0	0	0	0	0	0	0
Metabolic acidosis												
subjects affected / exposed	0 / 3 (0.00%)	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 8 (0.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 3 (0.00%)
occurrences all number	0	0	0	0	1	0	0	0	0	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2019	Inclusion of optional Study Part C. Change in dosage form to dry powder blend requiring dispersal in water prior to administration and inclusion of text concerning information provided to parents/carers as to how to prepare and record administration of IMP at home. Adjustment of minimum hospital stay to at least 3 days. Adjustment to RSV signs and symptoms to be monitored and how these will be analysed. Update to permitted concomitant medications. Update to assessments to include evaluation of hydration status. Clarification of duration of SAE reporting and SUSAR reporting commitment.

15 Jan 2020	Addition of central laboratory (ECG analysis). Addition of respiratory pathogen screen of baseline nasopharyngeal swabs using BioFire assay.
01 Mar 2021	Change to central laboratory responsible for viral resistance emergence testing. Reduction in nasopharyngeal swab sampling timepoints and rationalisation of PK sampling. Clarification of subject replacement parameters in all study parts. Update to study analysis populations and their definitions.
31 Jan 2022	Amendment to Part C study design, objectives, and endpoints. Clarification of requirements for opening Cohort 5. Clarification of informed consent requirements in line with local regulations. Adjustment to inclusion and exclusion criteria. Amendment to Part C duration of hospitalisation. Revision of stopping criteria, correction of adverse reaction definition, clarification of AE severity grading and AE Part C follow-up duration in response to regulatory request. Amendment to prior and concomitant medication section to clarify permitted medications/therapy and update to list of drugs affecting CYP3A4 and P-gp. Introduction of ReSVinet Scale for Clinicians in Part C. Clarification of study procedures and permitted time windows. Clarification of information to be provided to the parent/carer at discharge. Clarification of local laboratory and central laboratory safety testing. Updated monitoring section to reflect changes in monitoring during COVID-19 pandemic.

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055600

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4184 A61P31/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2016/055780 A1 (RE VIRAL LTD [GB]) 14 April 2016 (2016-04-14) page 23 - page 24; claims 1, 15, 18; example 1	1-16

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2024	05/08/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bergkemper, Victoria

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/055600

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DEVINCENZO JOHN ET AL: "A Randomized, Placebo-Controlled, Respiratory Syncytial Virus Human Challenge Study of the Antiviral Efficacy, Safety, and Pharmacokinetics of RV521, an Inhibitor of the RSV-F Protein", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 64, no. 2, 27 January 2020 (2020-01-27), XP093189544, US ISSN: 0066-4804, DOI: 10.1128/AAC.01884-19 Retrieved from the Internet: URL:https://journals.asm.org/doi/pdf/10.1128/AAC.01884-19> abstract page 9 -----	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2024/055600

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