CHIMP: Effect of intranasal administration of palivizumab on experimental respiratory syncytial viral infection – a controlled human infection study

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PROTOCOL TITLE: Effect of intranasal administration of palivizumab on experimental respiratory syncytial viral infection in a controlled human infection model

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
ISC	**Independent Safety Committee**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Globally respiratory syncytial virus (RSV) is the second cause of death after malaria in infants. RSV immunoprophylaxis with palivizumab is prohibitively expensive and only administered to high risk children in developed countries. There is a need to make palivizumab affordable through local administration. We established preclinical proof of concept in mice: intranasal (IN) palivizumab provides full protection against RSV for at least a week after administration. We tested the stability and shelf-life of a palivizumab in nose drop formulation. In a phase I double-blind RCT we showed safety in healthy adult volunteers. This study will provide clinical proof of concept that IN administration will block RSV at the point of entry (Bouncer Hypothesis) in experimental human infection. To mitigate the risks of large and costly late-stage trials, an RSV controlled human infection model (CHIM) allows for a rapid proof of concept that is also cost-effective to test for efficacy of the proposed IN administration at an earlier stage. The World Health Organization (WHO) has determined that CHIM contributes vital scientific knowledge and can significantly accelerate clinical development.

Objective:
Study A: Validation of productive infection of RSV CHIM
Study B: Effectiveness and immunogenicity of local administration of palivizumab on prevention of experimental RSV infection

Study design:
Study A: Validation of RSV CHIM in healthy adult volunteers: Productive infection in RSV CHIM; after evaluation study B will start based on decision of PI. The ethics committee will be informed of the decision to continue prior to Study B.
Study B: Phase II RCT: Non-therapeutic double-blind placebo-controlled proof-of-concept trial of RSV prevention through IN administration of palivizumab or placebo in healthy adult volunteers

Study population: Study A and Study B: healthy adults aged 18 – 55 years with no children <3 years of age or other high-risk individuals in their household (n=6 and n=28 respectively).

Intervention (if applicable):
Study A: No intervention, only viral challenge.
Study B: 0,1mL nose drops (1mg/mL palivizumab or placebo) administered per nostril one time as a prophylaxis 2 hours before the viral challenge

Main study parameters/endpoints:
Study A:

1. Productive RSV infection (defined as 2 positive viral detections by PCR assay on 2 consecutive sampling points during the quarantine, post RSV inoculation measured on day 2 onwards).

Study B will start if there is productive infection in at least 1/6 volunteers in Study A. See section 3.2 [Figure 2] for alternative pathway to study B if these criteria are not met.
Study B:

1. Area under the curve (AUC) for viral load as determined by quantitative PCR from a daily nasal-wash sample from day 2 to day 14 similar to previous studies (1, 2).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
Study A:

This is a validation study. There are two main risks of CHIM that should be considered (1) risk of severe infection in study subjects and (2) risk of transmission from experimentally infected individuals to researchers or the broader public. Healthy young adults do not suffer from severe RSV infection, but at most develop mild-to-moderate common cold symptoms after experimental RSV infection (1-3). RSV CHIM has been used safely in clinical trial settings to test antivirals (1). The potential risk of transmission of RSV from experimentally infected individuals to research staff and the wider public will be addressed using infection control standard procedures (droplet isolation) and will be monitored. These SOP's will be developed by the study team and approved by the Department of Infection Control at UMCU (Dr. Annet Troelstra and Dr. Herman Wunderink) before start of the study.
The burden of the study includes 10 days of inpatient quarantine (reduced to 7 days if PCR negative on day 7) as well as minimally invasive study procedures including viral inoculation, nasal sampling (nasal lavage, scrape, SAM, oral swabs, spirometry) and phlebotomy.
There is no direct benefit to patients who participate in the study.
Study B:
This is a non-therapeutic study. The main difference is that Study B will occur in the outpatient setting which will limit the burden of quarantine as participants will self-quarantine (7–10 days) in their home setting. Study A will be used to carefully evaluate and adjust measures as necessary to limit transmission risk in study B. Volunteers will be trained in transmission prevention measures and will be screened for children <3 years of age or other high-risk groups in the household. Minimal risk is associated with the IMP which have been previously evaluated by the Ethics Committee in the Narsyn trial. Additional safety data has been collected in the phase I and IIB trial. Risks are described in more detail in section 10.4. We have shown the IN formulation to be safe in a phase I trial in healthy adults. The burden includes study procedures that are non-invasive (nasal scrape, nasal washes, SAM, oral swabs and lung function measurements) and 7 blood draws. There is no direct benefit to patients who participate in the study.

1. INTRODUCTION AND RATIONALE

Respiratory Syncytial Virus (RSV) is a leading cause of lower respiratory tract infections in infants and is responsible for the majority of pediatric hospitalizations (4, 5). Furthermore, RSV poses a significant health risk to the elderly and immunocompromised (6, 7). A study published in the Lancet estimated that "globally in 2015, 33·1 million (uncertainty range [UR] 21·6–50·3) episodes of RSV acute lower respiratory illnesses resulted in about 3·2 million (2·7–3·8) hospital admissions, and 59 600 (48 000–74 500) in-hospital deaths in children younger than 5 years" (8). The same study estimates that the overall RSV-ALRI mortality could be as high as 118,200 in 2015 (8). Although there are risk factors, such as prematurity and congenital heart disease, that contribute to the likelihood that a child develops RSV, 80% of children hospitalized with RSV were previously healthy and did not have any recognized risk factors for disease (9, 10). RSV has been recognized by international organizations such as the World Health Organization (WHO) and Bill & Melinda Gates Foundation (BMGF) as a global health problem.

Despite increasing awareness and 50 years of research efforts, interventions are limited to supportive care and an effective vaccine against RSV does not exist (11). The ideal RSV vaccine must be a passive vaccine which is effective immediately after birth so that it protects an infant while it is most vulnerable to viral pathogens. However, the immature immune system of infants and high safety requirements at this age present challenges to the development of an intervention for this target population. Research has focused on interventions like maternal vaccination during pregnancy, which enables that transplacental transfer of RSV-specific antibodies from mother to infant, and passive immunoprophylaxis with an RSV-specific antibody given directly to the infant (12-14). Furthermore, the RSV maternal vaccine furthest along in clinical development failed to meet the primary endpoint in a phase III trial (14).

The only approved preventive intervention against RSV is palivizumab (SYNAGIS®), a humanized monoclonal antibody targeting RSV. Palivizumab is an existing clinical intervention for high-risk infants which is administered to prevent serious lower respiratory tract infections caused by RSV (12). By targeting the surface F protein of RSV, palivizumab has been shown to prevent 55-82% of RSV-associated hospitalizations (15). However, the problems associated with this intervention are four-fold: 1) it is prohibitively expensive, 2) the route of administration is via monthly intramuscular injections, 3) one in five children has a break-through infection at the end of the month, 4) hypersensitivity reactions, though very rare, are known to occur (12). Due to high costs, clinical use is limited to premature infants and other high-risk paediatric cases (4). Given the high disease burden, it is important to develop an alternative intervention which can be administered to all infants following birth.

We hypothesize that IN administration will provide a solution to these problems and allow palivizumab to become affordable, acceptable, safer and more effective. Intranasal (IN) prevention administered at the site of infection, the upper airways, may be key to preventing disease. In mice, we demonstrated that IN palivizumab provides full protection against RSV for at least a week after administration (16, 17). To develop the IN immunoprophylaxis, palivizumab was reformulated into nose drops. The safety of this investigational product was tested in a phase I double-blind RCT which showed that this formulation was safe in healthy adult volunteers (unpublished data, patent under review PCT/EP2020/069637). Furthermore, a phase IIb trial in healthy infants has been prematurely

terminated in 40 hospitals throughout the Netherlands after futility was concluded from an interim analysis (April 2021). The following study will test the prophylactic efficacy of IN administration of reformulated palivizumab in healthy adults infected with RSV-A Memphis 37 and will help provide information regarding dosing frequency, interval, nasal antibody half-life, pharmacokinetics, immunogenicity, expanded safety data and potential reasons for futility of the phase IIb trial.

The controlled human infection model (CHIM) will be used to demonstrate efficacy of IN palivizumab. In CHIMs, otherwise known as human challenge trials (HCTs), volunteers are infected with a well characterized pathogen to either study the pathophysiology of the pathogen or to test the efficacy of interventions against the pathogen, such as vaccines (18). The WHO has endorsed the importance of CHIM in clinical development of new therapeutics. According to the WHO, the ability to fail fast using CHIM "minimizes risk to human subjects by not conducting large efficacy studies" of interventions that would not prove effective. Furthermore, the WHO finds that CHIM "could result in significant cost- and resource-savings and could minimize lost opportunity costs by abandoning an unpromising candidate before committing greater expenditures to higher-phase clinical trials" (19). CHIM for pathogens of global consequence, like RSV, have been used for over 70 years to study the pathogenesis, microbiology, clinical symptoms, and immune response associated with well characterized pathogens (20). According to the WHO, CHIM studies are an important tool to limit costs of and accelerate the developmental process of new vaccines (19). Accordingly, we propose to implement CHIM for rapid and affordable proof of concept of IN palivizumab nose drops.

Limitations of historic human RSV challenge experiments (3)
Kravetz and colleagues first successfully infected 20 adult volunteers in 1961 with an RSV strain (Long) isolated in 1957 from a patient with bronchopneumonia. Since that time there have been numerous successful challenge studies of human RSV involving over 400 subjects using both wild-type and attenuated strains without reported serious adverse events. Valuable knowledge about the route of infection, incubation periods, durations and determinants of protective immunity, and duration of viral shedding has been gained from these studies, but much of what we have learned from RSV in mice was not investigated in these older studies. Many virus strains utilised in these studies are no longer available for human use due to increased regulatory stringency.

RSV Memphis 37: a low-passage, GMP-manufactured viral inoculum (3)
The historic human RSV challenge studies have used virus strains isolated by serial laboratory passage in multiple cell lines or live-attenuated strains. Successful infection has required the use of high doses and is often minimally symptomatic, suggesting that viral strains are extensively laboratory-adapted and likely attenuated. This poses a significant problem when trying to accurately reproduce and study natural infection.

RSV Memphis 37 is an inoculum developed specifically for CHIMs. It was isolated from a natural infection occurring in a neonate in the US by plaque purification in human vero cells (5 passages only) under fully GMP-compliant conditions. It was then tested according to appropriate ICH and FDA guidance documents for the production of a human clinical vaccine product. This virus has been used to infect 140 healthy adults in studies in the US without reported serious adverse events. Infectivity in humans has been demonstrated for doses of 3-5 log pFU.

In the last decade, 16 challenge studies of human RSV have been conducted. Out of the 16 identified studies, 12 used the RSV A Memphis 37 viral strain and 4 did not specify the strain of RSV used. The majority of these studies had populations of healthy adults below the age of ≈ 60 and required patients to be quarantined for approximately 12 days in designated clinical wards. 13 of the mentioned studies examined the efficacy of varied interventions against RSV, while 3 studies examined the pathophysiology or immune responses caused by RSV. Out of the 7 studies that had available results there were no serious adverse events. Five studies documented mild to moderate adverse events (urticaria, epistaxis, bilateral otitis media, upper RTI, pharyngo-laryngeal pain, vomiting, rhinorrhea, headache, decreased pulmonary function, diarrhea, GI discomfort) which occurred in both intervention and placebo groups after viral inoculation and were not thought to be related to viral challenge. The 2018 study of the oral antiviral JNJ-53718678 reported 3 AEs that motivated the subjects to drop out of the study before dosing (Appendix A). For detailed information regarding the study designs of previous RSV CHIM, study endpoints, and results of CHIMs conducted over the last decade see *Appendix A: Table 1*.

Risks generally associated with the CHIM

Healthy adult subjects will be recruited as they are best suited to tolerate inoculation of the Challenge Virus. Potential risks for the subjects are the following:

IN Virus Challenge

Severe complications of naturally occurring RSV infection tend to occur almost exclusively in infants, the elderly, and persons of any age with chronic co-morbidities and significant immune compromise. Infection of otherwise healthy adults is not associated with any significant complications. The study population and inclusion and exclusion criteria are carefully selected to exclude patients at risk of severe disease. The medical and nursing staff in the designated quarantine unit will monitor for and manage any symptoms. Furthermore, the study makes use of a GMP certified well-characterized viral RSV strain, Memphis 37, to ensure safety of participants. It is unlikely that any subject enrolled in the study will transmit the Challenge Virus to their close contacts after the Challenge period (day 0 – 10) ends in Study A or Study B. After inoculation, the virus will be present in the subjects' nasal passages for several days but is not expected to be present by day 10. Study participants will be released from quarantine on day 7 if there is no evidence of infection.

Study procedures

Some study procedures may cause some discomfort and are described in the Patient Information Folder (PIF), these include:

- Blood drawing: this causes momentary pain, sometimes a bruise, occasional light-headedness and rarely, infection or fainting.
- Spirometry: the volunteer needs to blow hard multiple times (as per UMCU Operating Instruction). This procedure may make the volunteer cough or feel short of breath during or after the test.
- Nasopharyngeal washes: the act of flushing out the nose can be uncomfortable, causing sneezing or watery eyes.

- Nasal scrape: a small, soft-tipped plastic scraper will be used to scrape a piece of epithelium from the inner lining of the nose. The act of scraping the nose can be uncomfortable, causing sneezing, watery eyes, or in rare cases some nasal bleeding.
- Nasosorp: a small, soft-tipped thin absorptive paper will be inserted into one of the volunteer's nostrils for one minute. This process may be uncomfortable, but it should not be painful.
- Oral Swab: foam swab will be run across the gums and inside of the cheek by study participants for two minutes. Saliva is collected by rubbing the soft sponge swab along the gums. This procedure is non-invasive and should not be painful.

These conditions normally resolve without further problems. If the volunteer agrees, the screening doctor will provide the volunteer's General Practitioner (GP)/Doctor with a referral letter. There may be risks that are unforeseen and not anticipated. Every effort will be taken to monitor the health of the study participants to ensure that such risks are minimized.

2. OBJECTIVES

Study A:

Primary Objective:

1. Productive RSV infection, defined as 2 positive viral detections by PCR assay on 2 consecutive sampling points during the quarantine, post RSV inoculation measured on day 2 onwards. We will proceed to study B in the case there are at least 2/6 productive infections.

Secondary Objective(s):

1. To understand RSV transmission by performing RSV PCR on nasal samples from study personnel and fomites (faucet, handle to flush toilet, doorknob and light switch) before and after wiping these surfaces with alcohol on day 7 post inoculation [(nasal) swabs].
2. Safety measured by self-reported and physician-reported local and systemic adverse events, and severe RSV disease defined as lower respiratory tract infection with PCR-confirmed RSV that requires hospitalization or ICU admission
3. To characterize leukocytes pre- and post-inoculation [nasal scrape].
4. To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption].
5. To measure microneutralization of RSV-antibodies pre and post inoculation [blood].
6. To measure lung function over time pre and post inoculation (Peak Expiratory Flow, FEV1, FVC, and FEF25-75) [spirometry].
7. To measure safety by self-reported and physician-reported local and systemic adverse events, and severe RSV disease defined as lower respiratory tract infection with PCR-confirmed RSV that requires hospitalization or ICU admission
8. To measure symptom profile over time in study participants.

Study B:

Primary Objective: The primary aim of this study is proof-of-concept of prevention of experimental RSV infection through IN administration of palivizumab as measured by reduction in AUC of viral load as determined by quantitative PCR from a daily nasal-wash sample from day 2 to day 14.

Secondary Objective(s):

1. To define local and systemic safety of IN administration of palivizumab.

2. Measure pharmacokinetics and pharmacodynamics of palivizumab in serum and nasal washes.
3. To measure anti-drug antibodies (ADA's) to palivizumab.
9. To measure lung function over time pre and post inoculation (Peak Expiratory Flow, FEV1, FVC, and FEF25-75) [spirometry].
4. To characterize leukocytes pre- and post-inoculation [nasal scrape].
5. To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption].
6. To measure microneutralization of RSV-antibodies pre and post inoculation [blood].
7. To measure symptom profile over time in study participants.

3. STUDY DESIGN

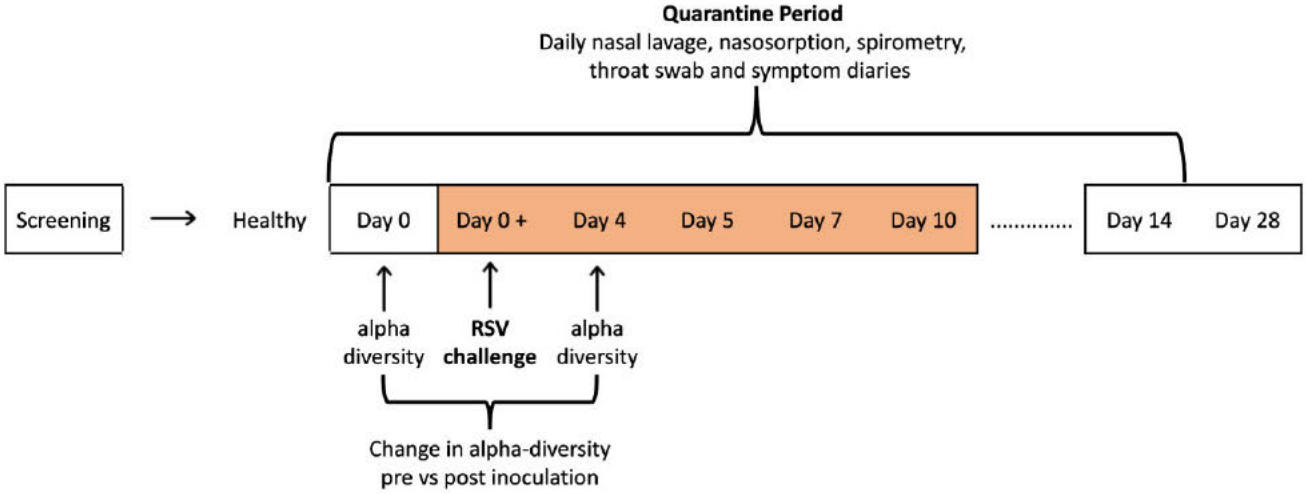
Study A will be an inpatient study which infects 6 volunteers with the challenge virus (RSV) to measure viral replication and the presence of RSV on fomites in the inpatient setting (Figure 1). Patients will be quarantined and in a designated unit in the WKZ to confirm that the study model effectively infects healthy volunteers with RSV before proceeding to study B. For continuation to study B, at least 1/6 patients must have a productive RSV infection after inoculation and there may not be viral challenge-related severe adverse events. We have chosen a minimum of 33% infection rate based on an expected RSV attack rate of the Memphis b37 strain of 55-60% without pre-screening for serum neutralizing antibody titres (personal communication, Chris Chiu (21)). The choice to perform study A is to validate the RSV CHIM by showing RSV infection is possible before proceeding onto a more costly study with more infected patients.

Study B will be the controlled human infection model, in which 28 volunteers will participate and be randomly allocated to placebo or control groups [Figure 1]. Study B will be used to show proof-of-concept of prevention of RSV infection through IN administration of palivizumab. The choice of a randomized controlled trial design will allow for minimization of the effect of individual patient characteristics through random allocation to treatment groups. The choice to inoculate a minimum of 1 hour after administration of study intervention is based on the minimal expected half-life of IN palivizumab of 4 hours. The half-life of IgG in the nasal epithelial lining fluid is not well established but due to mucociliary clearance it is expected that it is substantially shorter than in serum. Half-life of IgG in the nose of mice was determined to be 4 hours (22). The choice of 0.9% commercial nasal saline drops, which only differ from the intervention by the active ingredient, was based on commercial availability. Immunogenicity of the anti-RSV antibodies will be repeatedly measured by antidrug antibodies (ADA) in the serum and concentrations of palivizumab in the serum and nasal washes over a 14-day period to define pharmacokinetics. We collect nasal samples for pharmacokinetic data through 14 days after inoculation as it is twice the expected duration of protection (7 days) based on in vivo studies of IN palivizumab administration (23). Finally, only possible immediate toxicity is anticipated as we expect to have already observed long-term toxicity in extensive clinical use with intramuscular administration. Self-reported symptoms according to the FDA scorecard and SAE's will be used as the main safety outcome. The figure below gives an overview of the proposed study design

***Figure 1**. Study Design: Day 0 = pre-inoculation on day 0, Day 0+ = time of RSV inoculation.*

3.1 **Recruitment**

3.2 **In line with recruitment strategies advised by collaborating partners from Amsterdam UMC, Radboud UMC and Imperial College London, we aim to recruit healthy adults including students using various strategies including but not limited to flyers, short pitches in university lectures, posters, and social media. Participants will be screened for comorbidities (via a questionnaire) and general wellness (via a general health check-up to screen for serious medical conditions) on day -14 by a physician. We will not screen study population for RSV neutralizing antibody titres (I.e., Screen for participants in the lowest 10th percentile of RSV neutralising Ab titres). This pre-screening is known to increase the virus attack rate by approximately 10% (personal communication, Christopher Chiu, Imperial College;**



DeVincenzo NEJM 2014). We have decided not to perform screening due to costs, resources, patient burden and possible introduction of bias by selecting for participants with low immunity to RSV.Quarantine and Challenge

Study A:

Viral Challenge: On day 0, volunteers will be experimentally infected with 0.2 mL of 10^4 plaque-forming-units (PFUs) of RSV-A Memphis 37b. RSV infection will be confirmed by quantitative PCR from samples collected through nasal washes. We will use a phased approach to mitigate for safety risks and to account for capacity of study personnel to adequately be able to perform study procedures: the first participant will start on day 1, then the next 2 on day 2, and the next three on day 3 (n=6).

Follow up: We will perform nasal lavage, oral swab, nasosorption (alternating nostrils), and spirometry daily; nasal scrape (alternating nostrils), and blood draws at selected timepoints.

Quarantine: In study A, quarantine will be inpatient in a designated quarantine unit of the WKZ. Hygiene procedures (droplet isolation) for this unit will be adhered to and SOP's developed together with the Department of Infection Control at UMCU (Dr. Annet Troelstra and Dr. Herman Wunderink). Hygiene procedures outlined in the protocol have also been

reviewed by the Department of Virology/ Department of Infection Control at UMCU (Dr. Riezebos-Brilman).

Study participants will remain in quarantine for a minimum of 7 days and a maximum of 10 days. If a study participant has a negative RSV test on day 7 they can be released from quarantine on day 7 and study procedures will continue in the home setting. Otherwise, patients are released from quarantine on day 10.

For the following three scenarios in which criteria to move on to study B are not met, we have designed contingency procedures:

1. If study participants drop out, study participants will be replaced due to the small sample size in Study A.
2. If less than 1/6 study participants are productively infected with the challenge virus, then Study 2A will be conducted. Study 2A will be identical to study A, but the study population will be pre-screened for RSV neutralizing antibody titres. Only participants in the lowest 10th percentile of RSV neutralising Ab titres will be included in the study. This pre-screening is expected to increase the virus attack rate by approximately 10% (personal communication, Christopher Chiu, Imperial College; DeVincenzo NEJM 2014). The screening is not done in the first place due to costs, resources and patient burden.
3. In the case that 1/6 participants are infected, we will continue directly to study B but prescreen participants with low anti-RSV Ab titers and recruit participants in the lowest 10th percentile of neutralising Ab titers for participation in study B.
4. If all measured fomites are positive for RSV also after disinfection at a viral load high enough for human inoculation, then we will adjust the hygiene SOP and personal protective interventions for self-quarantine together with the department of hygiene to minimize the risk of viral transmission (see further description on p.20).

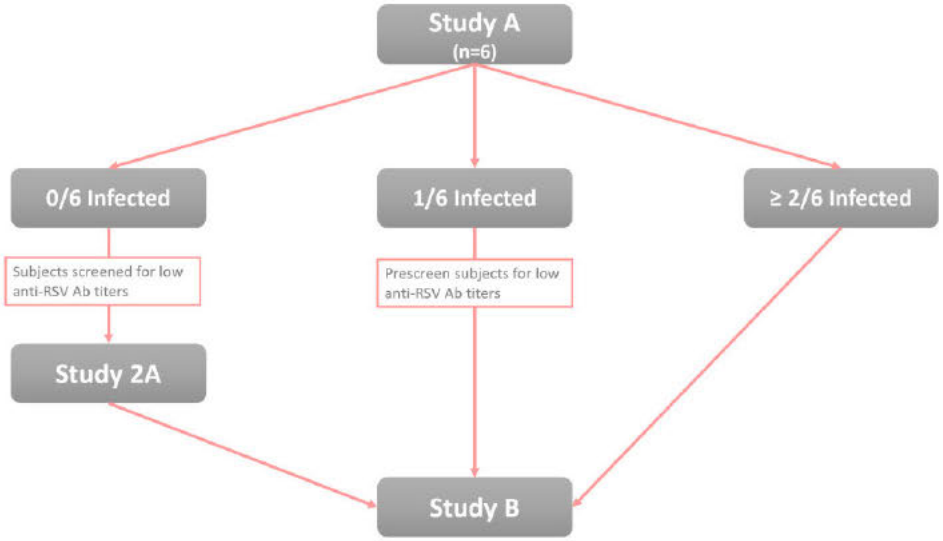


Figure 2: Control process for progression from study A to study B

Study B:

Intervention & Viral Challenge: On day 0 volunteers will be treated with 0.2mL nose drops divided over 2 nostrils (1mg/mL palivizumab or placebo), which will be administered at home

by study staff. Minimal one hour after administration of the nose drop volunteers will be experimentally infected with 1mL 10^4 plaque-forming-units (PFUs) of RSV-A Memphis 37b.

We will use a phased approach to mitigate for safety risks and to account for capacity of study personnel to adequately be able to perform study procedures: the first four volunteers will start on day 1, then six on day 2, 3, 4, and 5 (n=28). Collection of patient samples will occur via home visits.
Follow-Up: Daily nasal washes, nasosorp, spirometry. Blood draws on day 0, 1, 2, 3, 4, 7, 10, 14, 28 and nasal scrape on day 0, 3, 7, 10 and 14. Collection via home visits. The study visits at home will include a question whether housemates have experienced any symptoms.

Quarantine: In study B, quarantine is outpatient. Thus, quarantine includes a period of 7-10 days of self- quarantine at home. If a volunteer has a negative PCR (measured with molecular point-of care test, ID-now) on day 7 he or she may terminate the self-quarantine. If the volunteer has a positive PCR result, then he or she must remain in self-quarantine until day 10.

Routes of RSV Transmission & Preventative measures:
The guiding principle of our research is to use Study A to make Study B as safe as possible in the outpatient setting. One of the first things that must be addressed is the risk of transmission in the outpatient setting. According to research by Dr. Caroline Hall, RSV transmission occurs through direct contact with contagious secretions (24, 25). RSV can survive extracorporeally 6 to 12 hours on non-porous fomites, such as countertops, and doorknobs, and for less time on fomites like clothing (24, 25). A study by Madge et al. compared precautionary measures including gowns and gloves, cohorting, cohorting nurses plus gowns and gloves, and no precautions against RSV. This study demonstrated that cohort nursing with gowns and gloves was the only effective measure which significantly decreased the transmission of RSV in nursing infants (26). Furthermore, other research has promoted the use of strict hygiene, isolation of infected patients, education of clinicians and patients, gowns, gloves, masks, and even goggles (25). Thus, our safety efforts should aim to prevent direct contact between volunteers with RSV infections and non-infected people. In order to do so we will implement droplet isolation conform with hospital procedures and self-quarantine measures conform with RIVM guidelines for COVID-19.

To assess the risk of RSV transmission, we will measure the risk of RSV transmission by swabbing fomites at the peak of viral load during quarantine in study A (day 7) to test for the presence of RSV by qPCR. These measurement procedures were demonstrated in a 2010 study by Pappas et al (27). Then we will measure the effect of cleaning procedures by swabbing fomites before and after cleaning with alcoholic wipes. If these fomites are RSV positive, qPCRs will be performed. Our safety endpoint for qPCR is a viral load 10 times less than the viral load necessary for adult inoculation (10^2 PFUs). If analysis indicates that the viral load on fomites is less than or equal to 10^2 PFUs of RSV, then the risk of transmission is low enough to continue with study B in the outpatient setting using PPE measures. However, if the viral load measured on fomites is greater than 10^2 PFUs of RSV, then hygiene SOPS will be revisited together with the Department of Hygiene. Please refer to figure 3 below.

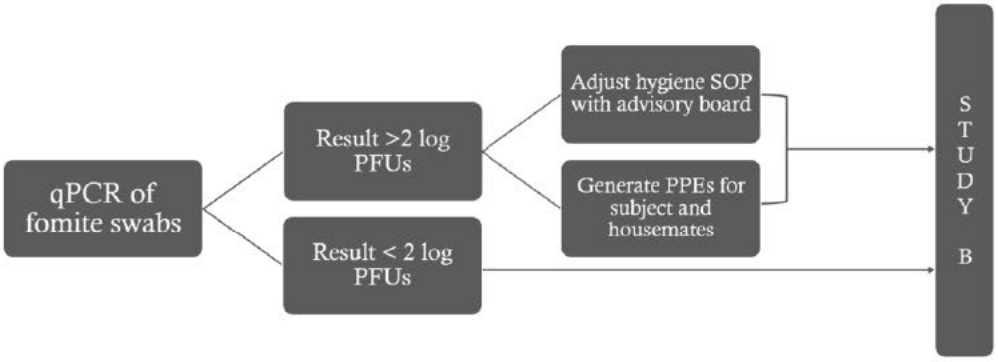


Figure 3: Flowchart of actions taken regarding after measuring viral load on fomites.

To diminish the risk of local transmission we will:

1. educate personnel and volunteers about the characteristics, transmission, and risk of RSV infection before starting the study
2. personal protective equipment (PPE) recommendation:
    a. handwashing
    b. gloves for staff and volunteers
    c. gowns for staff
    d. surgical masks for staff and volunteers
3. isolate infected patients: inpatient quarantine in study A in 1-person rooms and self-quarantine in the outpatient setting for study B (including keeping 1,5m distance from household members in home situation). House mates who show any symptoms of respiratory tract infection will be RSV POC tested immediately.

Study B is conducted in the outpatient setting and volunteers are self-quarantined at home. In this case, we suggest that the infected volunteers should wash hand thoroughly and prioritize hygiene by washing their hands often. For the duration of the self-quarantine, we advise that the infected volunteer has no direct contact, such as kissing or hugging, with the members of their household. Infected individuals are required to sleep in a separate bed. During follow-up we will monitor whether household members develop viral URTI symptoms.

For more information regarding transmission and prevention of RSV infection please see **Appendix E.**

3.3 Follow up

After infection, participants will self-quarantine for a period of 10 days. Follow-up will occur 14 -28 days after infection. During the quarantine period, patient samples will be collected via home visits:

- Blood draw
- Daily nasal wash, nasosorp
- Daily spirometry
- Nasal scrape
- Oral swab

In study B the main follow up measure will be PCR analysis of daily nasal lavage which will be performed during follow-up visits at home.

In study B, the immunogenicity of palivizumab nose-drops will be repeatedly measured through nasal washes and blood samples which will be collected during quarantine to define antidrug antibody (ADA) levels. The concentrations of palivizumab in serum and nasal washes will be measured over time to determine its half-life. Self-reported symptoms, according to the FDA scorecard, and SAE's will be used as the main safety outcome.

4. STUDY POPULATION

4.1 Population (base)

The study population for study A and B is the same. Healthy adults aged 18-55 years will be recruited, including students Included subjects must be of good health and they must not have a history of major medical conditions. To ensure no viral co-infection with COVID-19, we will test study participants for COVID-19 infection 48 hours before study start.

We will not screen volunteers based on pre-existing immunity because there is not medical risk associated with IMP administration, screening would be an extra intervention, and screening is costly. The risk of a volunteer having an adverse reaction from the IMP is minimal, as proven by 20 years of safe usage in a clinical setting. Thus, the extra cost and time needed to screen for pre-existing immunity is not warranted because there is little to no risk associated with IMP administration, whether or not the subject is infected with RSV. There is an increased burden to screen potential study participants as approximately 13 patients need to be screened to increase the infection rate by 10%. Furthermore, screening for pre-existing immunity towards RSV biases the study towards participants with a weaker immune response, reducing the generalizability of study results. (21)

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Healthy males or females
2. Age 18-55 years
3. Signed and dated informed consent form

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Child < 3 years old living in subject's household
2. Person > 65 years old or significant primary or secondary immunodeficiency living in subject's household
3. Presence of significant acute or chronic medical illness that is associated with increased risk of respiratory viral illness related complications. These include but are not limited to:
    a. Recent (within adulthood) history of asthma, chronic obstructive pulmonary disease (COPD), hypertension, reactive airway disease, or any other chronic lung illness

   b. History or evidence of impaired immune responsivity or autoimmune disease
   c. Confirmed hepatitis B (HBV), human immunodeficiency virus (HIV), or hepatitis C (HCV) infection
4. Adults with a nasal cold or obstructions which could interfere with administration of the study intervention
5. Simultaneous use of other nasal drops, sprays, or medications
6. Nasal surgery prior to or during the trial
7. COVID-19 infection 48 hours before study start
8. Pregnancy
9. Symptoms of clear nasal congestion

4.4 Sample size calculation

Study A: According to Imperial College productive infection occurs in 55-60% of volunteers after viral challenge. A sample size of 6 patients was based on costs and feasibility. No formal sample size calculation was performed. However, if we enrol 6 participants, we expect <1% chance that no infections will occur.

Study B:
Our sample size calculation is based on the following reasoning and assumptions. Our primary outcome measure is the amount of viral load measures repeatedly over time within an individual participant. The overall viral load will be summarized through the Area under the viral load curve (AUC). In each arm of the trial the distribution of AUCs will be a mixture due two different subpopulations: a proportion of participants in whom there will be no viral load (AUC=0) because the challenge did not lead to infection (expected proportion in the placebo group 45) and in the prophylaxis group we of course expect again 45% plus an additional proportion in whom prophylaxis prevented infection. In the remaining participants in whom infection did occur (AUC≠0), we expect the AUC under the log transformed values to be normally distributed with a certain mean and standard deviation (SD).

Because of this relatively large proportion of participants with an AUC=0, the distribution of the AUC in each arm will be extremely non-normal, and non-parametric testing needs to be performed to demonstrate a difference in distributions between the two arms using the Mann-Whitney test

Our sample size calculation is based on the following assumptions:
Placebo group:

45% will have an AUC=0 (expected proportion in whom infection will not occur). This assumption is based on an expected 55-65% infection in the placebo arm based on two CHIM trials published in the New England Journal, n=65 (DeVincenzo, NEJM 2015) and n=137 (DeVincenzo, NEJM 2014) as well as personal communications with Chris Chiu and Peter Oppenshaw (Imperial College), two experts in RSV human challenge trials.

- In the remaining 55% the mean AUC under the log10 PFU x hr/ml will be around 500 with an SD of 200 (Devincenzo NEJM 2015)

Prophylaxis group:
It is expected that prophylaxis wil lead to the following changes:

the proportion of participants with an AUC=0 will increase from 45% to 90%. We expect abortive infection (effect size close to 100%) as palivizumab is expected to prevent viral replication in the upper airways. To ensure sufficient power, we used a more conservative estimate of the expected effect size, assuming that the proportion of patients without infection will increase from 45% in the control arm to 90% in the treatment arm.

- In the remaining 10% the mean AUC under the log10 PFU x hr/ml will be lowered to 200 with an SD of 75

To demonstrate a difference in distribution in AUC between these two arms using a Mann-Whitney test with a power of 80% and a two-sided alpha of 5% requires a total of 14 participants in each group. These numbers are based on simulations using 5000 Monte Carlo samples based on the mixture of distributions described above.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

0.2mL of the 1mg/ml palivizumab nose drop (Narsyn) is administered as a prophylaxis 2 hours before the viral challenge.

Please refer to IMPD section 2.1. The rationale for the two-hour time period is based on expert opinion; two hours is considered the minimum time for a clinically valuable proof-of-concept. Furthermore, we consider two hours to certainly be less than the minimum expected half-life of 4 hours. A period of two hours will allow for distribution of the study intervention over the epithelial lining fluid of the nose.

5.2 Use of co-intervention (if applicable)

The use of co-mediation is allowed. There are no known interactions of palivizumab with other medications. However, as stated in the exclusion criteria, use of intranasal administered medications is not allowed.

5.3 Escape medication (if applicable)

Research indicates that cases of anaphylactic reaction to palivizumab are very rare. Anaphylactic reactions to palivizumab will be treated according to the Advanced Life Support guidelines. In the outpatient setting qualified personnel will observe a participant for the first 30 minutes after prophylaxis in order to be able to provide appropriate care.

6. INVESTIGATIONAL PRODUCT

The following sections were adapted from the Narsyn protocol (29).

6.1 Name and description of investigational product(s)

Narsyn nasal drops contain 1 mg/mL of palivizumab (Synagis; Abbvie B.V., Hoofdorp) diluted in 0.9% NaCl commercial nasal drops (Fagron NL BV; Capelle aan den IJssel). Palivizumab is a monoclonal antibody being developed for IN administration for the prevention of respiratory syncytial virus (RSV) infection during the first RSV season in a clinical trial. Currently

palivizumab is approved for intramuscular administration [1]. However, IN administration could allow administration at a significantly reduced cost (at least 90% reduction) that is more patient-friendly (needle-free) and expected to be more effective against RSV (administered directly to the site of action).

Palivizumab, both powder and solvent formulation, was approved by the United States (U.S.) Food and Drug Administration (FDA) in 1998 (BLA #103770)[2] and the liquid formulation (BLA 103770/S-5059)[3] was approved in December 2004 for intramuscular use. The EMA approved palivizumab powder formulation (EU/1/99/117/001 & EU/1/99/117/002) and the liquid formulation (EU/1/99/117/003 & EU/1/99/117/004) in 1999 for intramuscular use[4]. In fact, palivizumab has been licensed in 50 countries worldwide[1]. The product has a well-established safety profile from well-designed phase III clinical trials and more than 20 years of safety data from post-marketing surveillance.

Palivizumab has been evaluated in 6 clinical studies involving healthy subjects to determine the safety and tolerability profile and to assess the pharmacokinetic behaviour of the compound[1]. In addition, early clinical development included three Phase I/II studies in high-risk children (with prematurity, bronchopulmonary dysplasia (BPD)) to evaluate dose finding and mode of administration (IV v IM)[1]. Palivizumab was evaluated in 1 Phase III study in high-risk children (with prematurity, BPD)[5] and two other randomized placebo-controlled trials[6,7]. Liquid formulation showed a similar safety profile to the powder formulation in two clinical studies conducted to directly compare liquid and lyophilized formulations of palivizumab and two clinical studies in which the liquid formulation was used as an active control[8].

6.2 Summary of findings from non-clinical studies

Please refer to IMPD Section 2.2

6.3 Summary of findings from clinical studies

Please refer to IMPD Section 2.3

6.4 Summary of known and potential risks and benefits

Palivizumab is a monoclonal antibody with an extensive safety profile in children after more than 20 years of post-marketing surveillance. The antibody has a non-human target (the F protein of RSV). In the proposed trial we plan to administer the drug directly to the site of action: the upper airways. Given the extensive safety profile and the fact that the drug has a non-human target we do not expect additional risks form IN administration. In fact, we expect that local administration may even be advantageous as it may avoid unwanted systemic side effects[15]. Furthermore, a pilot study of administration of anti-RSV immunoglobulins (IgG, RSV IVIG) via aerosol in pediatric patients (<6 months) demonstrated safety of IN anti-RSV IgG in 10 children[16]. In the late preterm population we have shown that palivizumab (i.m.) can reduce RSV-related hospitalization by 82%, medically-attended RSV infection by 80% and total RSV infection by 67%[1]. In the case of locally administered therapy we expect the benefit of therapeutic efficacy to be the same or greater. Furthermore, the proposed trial has been supported by the RSV patient advisory board who believe this trial is an important step to address the morally challenging prohibitive costs of palivizumab while at the same

time allowing for a more child-friendly intervention: nasal drops instead of monthly intramuscular injections.

In 2018 we performed a phase I cross-over safety study in health adult volunteers in which the DSMB determined the local administration of palivizumab to be safe. The phase IIb trial was initiated because there were no adverse events or severe adverse events that were treatment-related. As there were no treatment-related adverse events and no severe adverse events, the DSMB found the safety profile to be acceptable and gave a positive advice to continue on to the phase IIB trial. We have included the summary of results from the phase I safety study in **Appendix B**.

6.5 Description and justification of route of administration and dosage

The upper respiratory tract is the initial port of entry and site of infection for RSV. We propose to administer palivizumab via the IN route, directly to the site of exposure. In vivo we have shown that IN palivizumab administration (0.005-0.05 mg/kg palivizumab) administered into the lungs of naive wild-type BALB/c mice protected against RSV infection in a dose-dependent manner and that this protection lasted at least one week (29). We expect administration directly to the site of action to minimize unwanted systemic side effects and decrease the dose needed for efficacy, which will drastically reduce costs by more than 90%.
We intend to administer the IMP via a nasal spray instead of nose drops after showing stability and expect to add this to the IMPD and submit this via an amendment Q4 2020.

6.6 Dosages, dosage modifications and method of administration

Dose-ranging studies are not possible for this study because there is no sampling mechanism in the nasal cavity to measure an effective drug dosage by measuring trough antibody concentrations. Therefore, the administered dose was defined according to "best knowledge available" from clinical studies or levels of therapeutic efficacy, which were used for intramuscular dose determination for current market approval.

In cotton rats, 10^2 reduction in virus titer was achieved after administering 2.5mgkg^{-1} palivizumab i.v. or i.m. which corresponds to a serum concentration of 30ugml^{-1} at the time of virus challenge[31]. For preclinical and clinical development the dosing regimen of intramuscular palivizumab has been designed such that trough concentrations are minimally 30 µg/ml and ideally greater than 40 µg/ml (as a margin of safety for person-to-person variability) for clinical efficacy [32]. Research showed that dose-dependent increases in concentration of anti-RSV antibodies in bronchoalveolar lavage fluid (BALF) were 500-1000x less than steady-state plasma antibody concentrations [33,34]. Consequently, a protective dose of palivizumab on the airways may be presumed to be 500x less or 0,08 µg/ml than serum concentration for therapeutic efficacy. Epithelial Lining Fluid (ELF) of the respiratory tract is predicted to be approximately 2,5 mL/kg [35]. Nasal ELF is estimated to be 800 ul per nostril[36]. Thus, in order to achieve a minimal trough concentration of 0,08ugmr1 in 800ul, 0,064ug is needed per nostril as a minimal protective dose. In this study we administer nasal drops with a concentration of 1 mg/ml of palivizumab with 0,2 mL administered, resulting in a dose of 200 ug, easily above the minimal threshold needed for therapeutic efficacy. In this study, we have decided to administer a total dose of 2 nose drops (100ul) per nostril. During the phase I study we administered one nose drop per nostril in healthy

adults. In this study we have doubled this dosage to ensure proof-of-concept that nose drops can prevent experimental RSV infection. Additionally, we have chosen specifically for this dosage is because of stability; antibodies are less susceptible to degradation when stored at higher concentrations (ideally 1 mg/ml or higher) [37]. Finally, other therapeutic antibodies that have been used locally utilize doses 1/100th of the required systemic dose to allow for reduced costs and side-effects[15].

6.7 Preparation and labelling of Investigational Medicinal Product

Palivizumab was derived from a murine Mab and humanised by grafting of the complementarity determining regions (CDR) of the murine monoclonal antibody Mab 1129 into a human antibody framework with an lgG1 constant region. It is composed of two heavy and two light chains with a combined molecular weight of approximately 148,000 Daltons and has been extensively characterised. The production cell line is a well-established murine myeloma NS0 cell line.
All stages of antibody production from cell culture to harvesting, purification, formulation, filling and take place at Boehringer lngelheim Pharma KG, Germany. The preparation of both the investigational medicinal product and placebo will take place at Apotheek A15, Gorinchem, The Netherlands.
Narsyn 1 mg/ml palivizumab diluted in 0,9% NaCl nasal drops will be packaged in brown glass nose drop bottles with pipette top with a volume of 5 ml. As a placebo a physiological saline commercial nasal drop (0,9% sodium chloride, Fagron) with a volume of 5 ml will be used for IN administration. Nasal drops will be produced at A15 Pharmacy, certified for release and delivered to the UMCU Pharmacy. Upon receiving the IMP, UMCU Pharmacy will store the IMP. Study staff will pick up a nasal drop bottle at the UMCU Pharmacy and deliver it to the study subject in outpatient quarantine unit for Study B.

6.8 Drug accountability

Narsyn will be delivered by Apotheek A15 (Rotterdam) and stored at the UMCU Pharmacy (Utrecht). Drug accountability for IMP supply (receipt, return or storage) will occur by UMCU Pharmacy. IN administration will be performed by study staff.

7. METHODS

7.1 Study parameters/endpoints (2)

7.1.1 Main study objectives parameters/endpoints

Study A:

1. Productive infection (defined as 2 positive viral detections by PCR assay on 2 consecutive sampling points during the quarantine, post RSV inoculation measured on day 2 onwards).

Study B will start if there is productive infection in 1/6 volunteers in Study A. See detailed protocol for transition to Study B if these criteria are not met.

Study B:

2. Area under the curve (AUC) for viral load as determined by quantitative PCR from a daily nasal-wash sample from day 2 to day 14 similar to previous studies (1, 2).

7.1.2 Secondary study parameters/endpoints

Study A:

1. RSV transmission on fomites or via healthcare personnel as measured by PCR positive swabs
2. Safety measured by self-reported and physician-reported local and systemic adverse events
3. To characterize leukocytes pre- and post-inoculation [nasal scrape].
4. To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption].
5. To measure microneutralization of RSV-antibodies pre and post inoculation [blood].
6. To measure lung function over time pre and post inoculation (Peak Expiratory Flow, FEV1, FVC, and FEF25-75) [spirometry].
7. To measure safety by self-reported and physician-reported local and systemic adverse events, and severe RSV disease defined as lower respiratory tract infection with PCR-confirmed RSV that requires hospitalization or ICU admission
8. To measure symptom profile over time in study participants.

Study B:

1. To define local and systemic safety of IN administration of palivizumab.
2. Measure pharmacokinetics and pharmacodynamics of palivizumab in serum and nasal washes.
3. To measure anti-drug antibodies (ADA's) to palivizumab.
4. To measure lung function over time pre and post inoculation (Peak Expiratory Flow, FEV1, FVC, and FEF25-75) [spirometry].
5. To characterize leukocytes pre- and post-inoculation [nasal scrape].
6. To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption].
7. To measure microneutralization of RSV-antibodies pre and post inoculation [blood].

To measure symptom profile over time in study participants.

7.2 Randomisation, blinding and treatment allocation

Study B is a double blind study. All protocol-associated investigators, research nurses, site monitors, data management and biostatisticians will be blinded to treatment assignment. Randomization and blinding will be performed via the research electronic capture system randomization tool Castor EDC. The pharmacy will know which trial number is linked to which treatment intervention (palivizumab or placebo). The research investigators responsible for statistical analyses remain blinded until the end of the trial at which time the key will be linked back to the subject numbers.

7.3 Study procedures

Study A: Procedure Schedule														
Procedure	Days relative to viral inoculation (day 0)													
	-14	0	1	2	3	4	5	6	7	8	9	10	14	28
Screening	X													
Lung Function		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam for airway patency		X												
Blood samples		X	2X	X	X	X			X			X	X	X
Nasal Lavage		X	X	X	X	X	X	X	X	X	X	X	X	X
Nasosorption		X	X	X	X	X	X	X	X	X	X	X	X	X
Nasal Scrape		X			X				X			X	X	
Oral Swab		X	X	X	X	X	X	X	X	X	X	X	X	X
Virus Inoculation		X												
Symptom diary card		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4a. Study A Procedures Diagram*: This diagram shows which procedures will occur on which day throughout Study A. COVID test 48 hours before participation in trial is not included in this overview. Baseline measurements are carried out on day 0, 0 = pre inoculation. On day 1 the blood samples will be taken both in the morning and afternoon.*

Study B: Procedure Schedule													
Procedure	Days relative to viral inoculation (day 0)												
	-14	0	1	2	3	4	5	6	7	8	9	10	14	25
Lung Function		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam for airway patency		X												
Blood samples		X	2X	X	X	X			X			X	X	X
Nasal Lavage		X	X	X	X	X	X	X	X	X	X	X	X	X
Nasosorption		X	X	X	X	X	X	X	X	X	X	X	X	X
Nasal Scrape		X			X				X			X	X	
Oral swab		X	X	X	X	X	X	X	X	X	X	X	X	X
Virus Inoculation		X												
Symptom diary card		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4b. Study B Procedures Diagram*: This diagram shows which procedures will occur on which day throughout Study B. COVID test 48 hours before participation in trial is not included in this overview. Baseline measurements are carried out on day 0, 0 = pre inoculation. On day 1 the blood samples will be taken both in the morning and afternoon.*

Challenge Virus:

For further information regarding the safety testing, storage, transportation, dilution, and disposal of the challenge virus, see **Appendix C.**

Virus Inoculation

On the day of inoculation, virus stock will be defrosted on ice. The inoculation procedure will be performed using a neutral pressure room in the UMCU (Personal communication UMCU). Subjects will be inoculated using intra-nasal drops or nasal spray (Pfieffer Bidose – modelled after procedures are Imperial College) on a single occasion with inoculum at a given dose divided equally between the two nostrils. This will be done slowly with sufficient interval between each inoculation (2-3 minutes) to ensure maximum contact time between with the nasal and pharyngeal mucosa. Subjects will be

asked not to swallow during the procedure to ensure maximal pharyngeal contact. Following inoculation, advice regarding hand hygiene will be given and subjects will be provided with alcohol hand gel to reduce spread of virus in the environment.

Nasal sampling procedures

All nasal procedures will be performed in the order below. In Study B, all study procedures, including viral inoculation, will be performed during home visits by study staff [Tables 4a&4b].

Nasal scrape

Rhinopro® curettes will be used to obtain a sample of nasal epithelial cells from each nostril. This is a painless procedure and will not require local anesthetic. The following technique is used:

• The subject should be sat comfortably, ideally with their head fixed, looking forward, while their chin rests on a support (if available)
• Tear bag and remove the flexible plastic Rhinopro® without contaminating the scoop end
• Place a speculum in the nose to keep the cavity open and employ good lighting
• Under direct visual inspection, insert the cupped probe onto the surface of the mid-inferior portion of the inferior turbinate. Note: Avoid the anterior bulb.
• The Rhinopro® should be 3cm up the nose; the floor of the nostril can be used to rest on
• Have the cup of the Rhinopro® at the correct angle
• Gently press the cupped tip on mucosal surface and move out and in of nostril 3mm up to 3 times
• Note that this area has limited sensitivity and the subject should not find this procedure painful, although a nasolacrimal reaction usually occurs

The cell harvest is epithelial cells, goblet cells and mast cells. It does not contain deeper layers of the mucosa. The sample obtained should be placed immediately into a sterile 2mL centrifuge tube containing Trizol or RLT and frozen at -80°C for storage prior to analysis.

Nasosorption

Nasosorption is performed using the following technique:

- Applicator is unscrewed from tube. Patient's head is held with one hand and tip of nose is pushed back with thumb to provide a clear line of sight. With the aid of a light source, the nasosorption device is inserted into nostril. The absorbent strip is located flat against the surface of the inferior turbinate.
- The device is held in place with a nose clamp for 60 seconds
- Nasa clamp is released and applicator is removed from nasal cavity. Device is returned to tube and screwed back in.

Nasal lavage

Nasal lavage is performed using the following technique:

• 5mL of 0.9% saline is introduced into one nostril using a syringe attached to a nasal olive with the subject sitting with the head tilted forward
• The saline is then washed in and out of the nose approximately 20 times by alternately withdrawing and advancing the plunger of the syringe while the subject maintains a tight seal between the nasal olive and the nostril; the aim is to recover ~80% of the saline from the nose

• The fluid is then aliquoted into sterile microfuge tubes and centrifuged for analysis of cells

Lavage fluid will later be analyzed to quantify the degree of RSV shedding. Quantitative multiplex PCR will be performed on the pre-inoculation lavage and post-inoculation lavage collected during the study to exclude the presence of other common respiratory viruses (Blanken, NEJM 2013). Supernatants will be frozen and stored at -80°C.

Blood sampling

Study A:

Blood tubes for plasma and RNA extraction will be obtained on days 0, 1, 2, 3, 4, 7, 10, 14, and 28. Blood tubes for PBMC will be collected on day 0, 3, 7, 10, 14 and 28. Maximum blood draw on any single day will be 48,5mls and total blood volume will not exceed 267,5 mls over the 28 day study period (Table 1).

Study B:

Blood tubes for plasma and RNA extraction will be obtained on days 0, 1, 2, 3, 4, 7, 10, 14, and 25 (± 3 days). Blood tubes for PBMC will be collected on day 0, 3, 7, 10, 14 and 25 (± 3 days). Day 28 (Study A) has been changed into day 25 ±3 days because of logistic and feasibility reasons. Maximum blood draw on any single day will be maximum 48,5 mls and total blood volume will not exceed 267,5 mls over the 25 day study period (Table 2).

Table 1: Volume per tube (mls), number of tubes and total volume per day study A

Day (Volume per tube)	0	1	2	3	4	5	6	7	8	9	10	14	28	Totaal
Serum (10)	1	2	1	1	1			1			1	1	1	
RNA (2,5)	1	1	1	1	1			1			1	1	1	
PBMC (9)	4			2				3			2	2	2	
Total Volume	48,5	22,5	22,5	30,5	12,5			39,5			30,5	30,5	30,5	267,5

Table 2: Volume per tube (mls), number of tubes and total volume per day study B

Day (Volume per tube)	0	1	2	3	4	5	6	7	8	9	10	14	25 (± 3 days)	Totaal
Serum (10)	1	2	1	1	1			1			1	1	1	
RNA (2,5)	1	1	1	1	1			1			1	1	1	
PBMC (9)	4			2				3			2	2	2	
Total Volume	48,5	22,5	22,5	30,5	12,5			39,5			30,5	30,5	30,5	267,5

Sample storage

All collected samples will be stored and can be used for future research according to the Biobank protocol.

Portable Spirometry

Performing the measurement: Posture must be consistent during the measurements throughout the study, either standing or sitting, with no breathing limitation. The subject should breathe in to measure total lung capacity. A good tight seal by the lips round the mouthpiece is essential. The subject should then exhale forcibly into the spirometer, blowing as hard as possible and continue to residual volume. The best value of 3 attempts will be recorded.

RSV Rapid Test (ID Now)

Nasal swab for RSV rapid testing is performed using the following technique:

1. Personnel conducting nasal swab in study A must wear PPE
2. Enter a flexible swab several centimeters with a slow, steady motion along the floor of the nose (straight back, not up the nose) until the posterior nasopharynx has been reached (distance from nostrils to external opening of ear)
3. Place finger on the tip of the patient/resident's nose and depress slightly
4. Once resistance is met (the swab should pass into the pharynx relatively easily), rotate the swab several times and withdraw the swab
5. Break off top of swab (it will snap off)
6. Place in transport medium.
7. Remove personal protective equipment, wash hands.

Oral Swab

A foam, spongy swab will be used to collect saliva. This can be performed in any position comfortable for the subject. Remove the swab from the sterile container. Participants are asked to run the swab across the gums and inside of the cheek for two minutes. In a similar way as using a toothbrush. The procedure is non-invasive and should not be painful. After obtaining the sample place at room temperature until further analysis.

Clinical symptom scores

A self-completed diary card of both upper and lower respiratory tract clinical symptoms will be made at baseline and daily from day 0 until day 14 (see **Appendix D**).

Individual symptom scores will be accumulated over the 14 day period of quarantine or self-isolation after inoculation and the first few days of follow up (day 10 – day 14) Then, the baseline recording will be subtracted from the post inoculation recordings. Thus, for a patient who has a score of zero on day 0 prior to inoculation, the maximum cumulative score for the following six days is 144.

Upper Respiratory Tract Symptoms

A total 'upper respiratory clinical symptom score' will be derived using a four-point scale (0-3 for absent, mild, moderate and severe) for each of the following eight respiratory symptoms: sneezing, headache, malaise, fever/chills, nasal discharge, nasal obstruction, sore throat and cough according to the table in **Appendix D**. Volunteers can get a maximum clinical severity score of 24 per day. This is an established method for studies of common cold illnesses. Symptoms will be recorded at the same time of day and before any procedures such as nasal lavages are performed.

Lower Respiratory Tract Symptoms

A diary card of lower respiratory tract symptoms will be completed with a scoring system outlined in **Appendix D**.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Subjects withdrawn for safety reasons must be followed until resolution of complaints or at least until stabilization.

7.5 Replacement of individual subjects after withdrawal

Study A: We will replace individual subject after withdrawal due to the small sample size.
Study B: Not applicable

7.6 Follow-up of subjects withdrawn from treatment

Not Applicable.

7.7 Premature termination of the study

In case serious adverse events (SAE) or suspected unexpected serious adverse reactions (SUSAR) occur, these events will be evaluated. When a causal relation with the study is suspected or cannot be excluded, further inclusion for this study will be stopped. After an SAE in the phase I trial an independent committee will determine whether the SAE is likely to be causally related to the study medication. This committee will be defined before the start of the study.

7.8 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8. SAFETY REPORTING

8.1 AEs, SAEs and SUSARs

8.1.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / the experimental infection. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.1.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC

SUSARs that have arisen in the clinical trial that was assessed by the METC;

- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.4 Independent Safety Committee (ISC)

Not applicable

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

Study A: The primary endpoint is the percent of patients with productive infection (defined by 2 positive viral detections by PCR assay on 2 consecutive sampling points during quarantine, post RSV inoculation measured from day 2 onwards)

Study B: The primary endpoint is the AUC viral load as measured by the qRT-PCR assay from viral load measurement from day 2 through day 14. This analysis will be performed to test the null hypothesis that there is no difference between the Narsyn (IMP) and placebo treatment groups in the mean AUC viral load. For the primary analysis, a mixed-effects model with a repeated-measures approach will be implemented to allow for unequal variances.

9.2 Secondary study parameter(s)

Study A:
We will use a longitudinal mixed effect model to analyze the repeated measurements which can be considered a continuous outcome measure. We will fit a random intercept per participant to

take the correlation within subjects into account. We will add time as a categorical variable (dummy coding) as the number of time points is limited. From this model, we can estimate the mean (95% CI) at every time point and calculate the area under the curve over time for each subject and the overall group.

Study B:
Quantitative assessments of symptom scores, lung function, viral load (AUC), leukocyte numbers and inflammatory markers will be compared between study arms. These measures will be generated using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q2, minimum and maximum). Dosing regimens were individually compared with the pooled placebo group, and all comparisons were two-sided, with the level of significance set at 0.05. Differences will be analyzed using two-tailed t-tests or Wilcoxon signed rank test as appropriate.

9.3 Other study parameters

Not applicable

9.4 Interim analysis

Not applicable

10. ETHICAL CONSIDERATIONS

This study was promoted by the RSV patient advisory board (PAB) as they find the cost issue of palivizumab-mediated prevention morally challenging. Please also see letter of support **in Appendix F** from the RSV Independent Patient Advisory Board.

A human challenge study presents an unparalleled study design to answer questions in a controlled setting leading to the unique acquisition of scientific knowledge. The value of CHIM to accelerate vaccine development is increasingly visible: in de past decade there have been more than 120 CHIM publications and serious adverse events have been rarely reported. We would like to set up RSV CHIM at UMC Utrecht in an academic setting with the goal of establishing CHIM at a lower cost, greater flexibility and increased scientific focus. We do this in partnership with Imperial College who have been conducting RSV CHIM since 2010.

CHIM trials provide no direct benefit to participants yet provide a benefit to global population health. For this reason, CHIM only possible for infectious disease which are treatable of self-limiting. In this sense, the risk-benefit analysis is similar to a phase I trial in which healthy volunteers are exposed to risk without direct benefit. The justification for the study is the potential benefit of scientific knowledge gained and societal benefit. The acceptable risk is proportional to the potential societal benefit. Some argue that the risk should not be larger than risks taken in normal life (Hope, J Med Ethics 2004). The risk of transmission to the public is a secondary risk which can be minimized using quarantine procedures. Safety data for RSV CHIM is elaborately established for direct population and risk of transmission well characterized. Furthermore, risk is minimal in comparison to risk in normal daily life. Below we have outlined the reasons that knowledge gained from CHIM is unique and not possible via a different study design:

(1) <u>Knowledge gained from CHIM is essential and distinct from phase IIb trial</u>

a. If the phase IIb trial results are negative and the current (CHIMP) trial is positive (showing proof-of-concept of intranasal prophylaxis) then clinical development of this affordable drug will not be stopped by default. The CHIMP trial may provide explanations for the failure of the phase IIb trial:
    i. Compliance: In the case participants of the phase IIb trial administer drug in the morning as opposed to the evening this may decrease efficacy if the half-life is <12 hours
    ii. Adherence: In the case participants miss drug critical drug doses pre-exposure in the phase IIb trial. In contrast, the CHIMP trial is a controlled setting in which this will not be the case.
    iii. The drug may work in adults but not in children. Thus, drug development may still be continued for the elderly, a population with an important disease burden (Falsey et al, *N Eng J Med* 2005)
    iv. In the case the drug half-life is shorter than 12 hours, daily dosage may not be sufficient to prevent infection during the day.
    v. To collect local and systemic pharmacokinetic data of palivizumab after intranasal (IN) administration (Cmax, Tmax, T1/2)
    vi. To collect local & systemic immunogenicity data (anti-drug antibodies)
    vii. A successful RSV CHIM will allow for dose-finding studies in the future to allow for selection of optimal drug dosing by measuring pharmacodynamics

of study drug. Optimal drug dosing and interval can help to minimize drug costs.

viii. A large-scale clinical trial is resource prohibitive for dose-finding studies. An RSV CHIM allows for a small-scale trial and gives an indication of whether it is worth pursuing in larger study even if phase IIb fails.

ix. Data regarding optimal drug dose and interval are not being collected in the current phase IIb trial and can be used in design of a phase III registration trial.

x. All drug development has occurred in the academic setting without private funding. Rapid proof-of-concept via CHIM will allow for investment in preparation of a phase III trial and will ensure no delay in access to drug due lack of funding

xi. Our study may also provide information that is relevant for the development of prophylactic SARS-CoV-2 antibodies to be administered nasally (pharmacokinetics and anti-drug antibodies following intranasal mAb administration)

(2) No comparable alternative for study design of RSV CHIM. A human challenge study presents an unparalleled study design to answer questions in a controlled setting leading to the unique acquisition of scientific knowledge. The value of CHIM to accelerate vaccine development is increasingly recognized: in the past decade there have been more than 120 CHIM publications and serious adverse events have been rarely reported. In the development of new therapeutics, CHIM are used as a proof-of-concept and motivation for further investment by funders (Roestenberg et al, *Lancet Infect Dis* 2018). Examples of pivotal CHIM for vaccine development include the world's first malaria vaccine (EMA, EPAR 2018), the first live attenuated vaccine for influenza A (Clements et al, *Lancet* 1984), the first influenza antiviral drug (Jackson et al, *Antimicrob Agents Chemoter* 1963), and drug development for RSV drugs (DeVincenzo et al, *N Engl J Med* 2014 & 2015). As CHIM reduces costs and time to registration, it is an ideal route to reduce costs of a drug for resource-poor countries with high mortality and morbidity burden. The concept of fast failure in clinical development is important as it allows for reallocation of resources for scientific research and minimizes unnecessary exposure to study drug. The advantages of CHIM are highly relevant to the proposed trial which aims to develop an affordable prophylaxis for an infectious disease with a major global disease burden.

a. RSV CHIM offers a unique opportunity to test vaccines because it allows drug development to be streamlined (reduced cost, time and sample size) and immunological parameters can be measured and monitored intensively in the natural host pre- and post-infection. Thus, experts argue that RSV CHIM is essential to maintain momentum of RSV vaccine development (Habibi et al, Vaccine 2016).

b. Contrary to the argument of the local IRB, there is no viable alternative to CHIM to obtain the proposed knowledge (ie drug pharmacokinetics). Namely, in vitro assays cannot capture the complexity of RSV infection in the human respiratory tract. Although RSV infection can be induced in animal models, animal models involve non-natural host-pathogen combinations which limit extrapolation of findings to human disease on which to base a phase III trial and future drug development. Thus, RSV CHIM is essential to obtain key pharmacokinetic data of intranasal mAb

administration, immunogenicity data as well as dose-finding and optimization in the future.

c. CHIM occurs in a highly controlled setting, with the unique ability to monitor immune responses from the moment RSV infection occurs. This unique design allows monitoring of viral load, immune response, drug pharmacokinetics before and after infection, and drug immunogenicity over time in a way that cannot be done in a different study design.

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Study A: Healthy adult volunteers, including students will be recruited using social media, flyers, posters, short pitches during lectures and more. If healthy adults indicate interest in the study we will call them by telephone to explain the study, screen eligibility criteria and -if subjects are eligible- send participants the information folder about the study including an informed consent form. If eligible adults decide to take part in the study, then they are asked to first return an informed consent form to us.

Participants will have time to think and ask questions before giving consent.

Study B: Study B will use the same recruitment process as Study A.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

Study A:

This is a validation and safety study of RSV human CHIM. There are two main risks of CHIM that should be considered (1) risk of severe infection in study subjects and (2) risk of transmission from experimentally infected individuals to researchers or the broader public. Healthy young adults do not suffer from severe RSV infection, but at most develop mild-to-moderate common cold symptoms after experimental RSV infection [15]. The RSV CHIM has been used safely in clinical trial settings to test antivirals [4]. The potential risk of transmission of RSV from experimentally infected individuals to research staff and the wider public will be addressed using infection control standard procedures and will be monitored. These SOP's will be developed and designed with the support of the Department of Infection Control at UMCU (Dr. Annet Troelstra and Dr. Herman Wunderink)

The burden of the study includes 10 days of inpatient quarantine as well as minimally-invasive study procedures including viral inoculation, daily nasal sampling (nasal lavage, nasopharyngeal swab, and spirometry), and 10 blood draws. [Tables 4a&4b].

There is no direct benefit to patients who participate in the study. Indirect benefits include societal benefits such as increased knowledge on safety and pharmacology of the IMP which will allow for accelerated drug development of affordable and child-friendly RSV prevention. Increased knowledge

on safety and pharmacology of the IMP which will allow for accelerated drug development of affordable and child-friendly RSV prevention. Most importantly, a successful RSV CHIM will allow for dose-finding studies in the future to allow for selection of optimal drug dosing and interval to help minimize drug costs.

Study B:
This is a non-therapeutic study. The same safety considerations regarding viral challenge are considered risks for study B although Study A. The main difference is that Study B will occur in the outpatient setting. Measures will be taken to understand and carefully limit transmission risk in Study A. Furthermore, volunteers will undergo self-quarantine for a period of 10 days, be trained in transmission prevention measures as outlined above in the protocol and will be screened to not have children <3 years of age or other vulnerable individuals in the household to limit transmission of RSV. The risks of transmission and severe disease will be carefully monitored for CHIM in a step-wise approach (study A followed by B) [Figure 2]. The safety risks of CHIM are mitigated by safety committee evaluation of Study A to continue to Study B.
Risk Assessment IMP:
There are also risks associated with the IMP: We have shown the IN formulation to be safe in a phase I trial in healthy adults. Furthermore, palivizumab is a registered drug for intramuscular administration that has an excellent safety profile and has been used clinically in children for more than 20 years. We expect fewer side effects with IN than systemic administration. The risks of this study associated with IN palivizumab administration are considered to be minimal. We will continue to critically and carefully monitor for safety signals during the study.
The burden of the study includes 10 days of self-quarantine. Study procedures are non-invasive (nasal swabs, nasal washes and spirometry) except for 10 blood draws.
There is no direct benefit to patients who participate in the study. Indirect benefits include societal benefits such as increased knowledge on safety and pharmacology of the IMP which will allow for accelerated drug development of affordable and child-friendly RSV prevention. Most importantly, a successful RSV CHIM will allow for dose-finding studies in the future to allow for selection of optimal drug dosing and interval to help minimize drug costs.

Study A&B Potential Issues of Concern
We believe there is an minimal risk given extensive experience with RSV CHIM: Safety data for RSV CHIM is well-characterized. There are two main risks (1) severe disease in the study population and (2) risk of transmission. Generally, risk can be considered minimal as it is not elevated in comparison to risk in normal daily life.

a. Progression of RSV infection in RSV CHIM have been found to be reproducible and predictable after extensive experience. In the past decade 16 RSV CHIM trials have been conducted. The majority (12/16) of these trials were conducted with the same strain as we plan to use. The RSV-inoculum, RSV-A Memphis 37b strain, is GMP-produced. Since 1961, over 400 volunteers have been infected with RSV during CHIM, using both wild type and attenuated RSV without reported serious adverse events.
b. The proposed study risk is acceptable according to even the most stringent definition of acceptable risk. According to more conservative frameworks, the risk due to CHIM should be “minimal” or no larger than risks taken in normal life (Hope, J Med Ethics

2004). Furthermore, the acceptable risk threshold proposed in a framework specific to CHIM is more permissive than "minimal risk," namely: "no risk of irreversible, incurable or possibly fatal infections" (Bamberry et al, Public Health Ethics 2016). The maximum risk to study volunteers in RSV CHIM, a common cold, is not considered significant as it is part of normal life and thus falls under "minimal risk." Furthermore, maximum viral load and symptoms post experimental infection have been well-characterized. The burden of sampling is limited given the non-invasive nature of nasal sampling.

c. The risk of transmission to the public is a secondary risk which will be minimized using quarantine procedures modeled after previous RSV CHIM. The department of infection control and the department of virology at UMCU have co-authored the protocol and will help to design to SOP's to limit the risk of transmission of virus to the general public. Historically, there is no record of RSV transmission to the general public after RSV CHIM.
d. We have selected a study population with low risk of severe RSV using stringent inclusion/exclusion criteria. The selection of the study population (young healthy adults) is such that they are at most expected to acquire a common cold illness.
e. We plan to perform intensive monitoring of study participants. Medical staff is available during the inpatient RSV CHIM 24/7. Vital parameters (blood pressure, heart rate, saturation, respiratory rate and temperature) will be monitored. Subjects are followed up intensively during quarantine and afterwards. In the unlikely case of severe disease, potential harms of respiratory distress can be minimized as effects can be managed through respiratory support.
f. The proposed study population is lower risk than other international studies. In the UK, even high-risk adults are currently being enrolled in RSV CHIM, as the risk of complications is deemed acceptable in the context of the value of the scientific knowledge gained. Likewise, experimental infection with rhinovirus has been induced in high-risk adults with mild COPD and moderate asthma (Zhu et al, *Chest* 2014; Mallia et al, *Respir Res* 2006).

10.5 Compensation for injury

Risks of severe adverse events due to palivizumab injection are considered negligible. The safety of palivizumab has been investigated and verified in extensive research.
The investigator has a liability insurance which is in accordance with article 7 of the WMO.
The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

A compensation of 750 euros will be given to participate in study A , due to the inpatient quarantine, and 500 euros will be given to participate in study B . We consulted the RSV PAB who support the

likelihood of participation without compensation, please also refer to the letter of support from the RSV Independent PAB [**Appendix F**].

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Samples and information from questionnaires obtained from subjects will be de-identified and coded with a subject number only. The investigators will have access to this code. The independent researcher who safeguards the randomization will not have access to the source data. After the experiments all data will be stored for 25 years. There will be no mention of personal data, such as name, initials or birth date, in any of the published data. All the usual precautions to safeguard the privacy of subjects will be followed during the research. All procedures for data handling and storage have been described in the data management plan.

11.2 Monitoring and Quality Assurance

For the reliability of the research, at random samples of research data on paper files will be compared with data in the database. This will be done by the monitor involved in this research. These data can also be accessed by government researchers from the Health Inspection or the Medical Ethics Review Committee to ensure the quality of the research.

A periodical visit will be made by a monitor to discuss the progress of the clinical trial and review CRFs and original source documents with the study personnel for accuracy of data recording, and correspondence.

The investigator guarantees that the trial participants are aware of and consent that personal information may be reviewed during the data verification process as part of monitoring/auditing.

Other data quality assurance will occur through automatic data checks in the eCRF tool. Finally, the researcher will also perform data quality checks before analysis for normality and outliers to ensure that data quality is high. Please refer to the monitor plan for further details on monitoring of the study.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6 Public disclosure and publication policy

There are no restrictions for publication of the research data. Every effort will be made to publish the research data in a peer-reviewed journal in a timely manner.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

Yes: see SPC of the reference product Synagis.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Yes: reference product Synagis EPAR Scientific Discussion and IMPD. Furthermore, a pilot study of administration of anti-RSV immunoglobulins (IgG, RSV IVIG) via aerosol in pediatric patients (<6 months) demonstrated safety of IN anti-RSV IgG in 10 children[16]. A phase I study showed safety in 2018 [NTR7187; Appendix B] and an phase IIb study has showed no adverse safety signals [NTR7204].

c. Can the primary or secondary mechanism be induced in animals and/or in ex-vivo human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Selectivity for non-human tissue (site II of the F surface protein of RSV virus).

e. Analysis of potential effect

Clear dose-effect relation in virus neutralization at target dose of administered study drug.

f. Pharmacokinetic considerations

Expected to be equal to reference product. Refer to data from the adult healthy volunteers PK study with study drug and IMPD.

g. Study population

Healthy volunteers aged 18-55

h. Interaction with other products

None. Extensive stability data indicate no interaction with benzalkonium chloride or 0,9% NaCl. Please refer to IMPD.

i. Predictability of effect

Expected effect is similar to reference product Synagis. This has been extensively characterized after 20 years of clinical use. Data supports that anti-RSV site of action of the reference product is local and not systemic.

j. Can effects be managed?

Severe allergic reactions including very rare cases of anaphylaxis and anaphylactic shock have been reported following palivizumab administration. In some cases, fatalities have been reported. Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis

and anaphylactic shock, should be available for immediate use following administration of palivizumab (SPC Synagis).

12.2 Synthesis

There is no increased risk or safety concern expected for IN administration compared with the reference product Synagis for intramuscular administration. A proof-of- concept study of IN anti-RSV IgG is being performed in young infants. The small risk of developing severe hypersensitivity reactions will be managed by prolonged supervision for the first administration for study A and B. The study staff will be trained to recognize severe hypersensitivity reactions at an early stage and to call for an ambulance in case of this rare occasion Medicinal products for the treatment of severe hypersensitivity reactions, including anaphylaxis and anaphylactic shock, are available for immediate use following administration of palivizumab at the ambulance and at any emergency ward in hospitals in the Netherlands.

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14. Appendices

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Appendix A: Table 1. Summary of RSV CHIMs Conducted from 2010-2020

Title	RSV strain	Study design	Result
Viral load drives disease in humans experimentally infected with RSV **2010**	RSV-A Memphis 37 strain	Healthy volunteers (n = 35), in 5 cohorts, received increasing quantities (3.0-5.4 log PFU) of IN RSV. Subjects were quarantined for 13 days and observed for at least 1 day before RSV inoculation. Nasal washes for viral assays and cytokine measurements were obtained upon admission (Day 1) and 2x/day on days 1-12. Pulmonary function tests were performed daily. For upper respiratory signs and symptoms, a physician's daily directed physical examination (Days 1-12) and a 2x-daily subject-reported RSV symptom score card (Days 1-12) were completed. Mucus weights for each 24-hour period were recorded from Days 1-12. AEs were recorded through the Day 28 follow-up visit	77% of volunteers consistently shed virus. Infection rate, viral loads, disease severity, and safety were unrelated to quantity of RSV received. Symptoms began soon after initial viral detection, peaked in severity near when viral load peaked, and subsided as viral loads slowly declined. Viral loads correlated significantly with IN proinflammatory cytokine concentrations. Increased viral load correlated with increases in symptoms, physical examination, and amount of nasal mucus. All adverse events were mild or moderate in severity. One volunteer developed bilateral otitis media.
A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus **2010**	RSV-A Memphis 37	This study tested the antiviral activity of ALN-RSV01 in adults experimentally infected with wild-type RSV. 88 healthy subjects were enrolled into a randomized, double-blind, placebo-controlled trial. A nasal spray of ALN-RSV01 or saline placebo was administered daily for 2 days before and for 3 days after RSV inoculation. RSV was measured serially in nasal washes using several different viral assays. In cohort 1 (n = 8), patients got 75 mg/day of ALN-RSV01.	The proportion of culture-defined RSV infections was representing a 38% decrease in the number of infected patients given the IMP. The IMP was associated with a 95% increase in the number of uninfected subjects. The acquisition of infection over time was significantly lower in ALN-RSV01 recipients (P = 0.007 and P = 0.03, viral culture and PCR, respectively). Multiple logistic regression analysis showed that the ALN-RSV01 antiviral effect was

		In cohorts 2–6 (n = 80), patients got 150 mg/day of ALN-RSV01. Subjects were quarantined for 14 days. Patients were medicated (ALN-RSV01 or placebo) 32 h (day 1) and 8 h (day 0) before RSV inoculation on day 0.	independent of other factors, including pre-existing RSV antibody and IN proinflammatory cytokine concentrations. No serious adverse events → few number of moderate AEs which were equally dispersed between placebo and control. All AEs occurred after end of quarantine
RV568 - Viral Challenge With RSV (protocol) **2011**	Unspecified strain of RSV	A Randomized, Single-blind, Placebo-controlled, Parallel Group Study to Investigate the Effects of IN RV568 (400µg) Administered 2x Daily to Adult Male Volunteers Experimentally Inoculated With Live RSV	Results were not found. Study endpoints are listed below: IL8 induction in nasal wash samples [16 day quarantine period] RSV viral, Changes in symptoms of RSV infection Assessment of mucus weight and tissue counts, Viable nasal cell counts in nasal washes, Plasma RV568 levels, & Assessment of IL6 in nasal wash samples
Study of Single and Multiple Doses of ALS-008176 in Healthy Volunteers (protocol) **2013**	Unspecified strain of RSV	This is a Randomized, double-blind, placebo-controlled, first-in-human, 3-part study of orally administered ALS-008176 to evaluate the safety, tolerability, and PKs of single ascending dosing, multiple ascending dosing and food-effect in healthy volunteers. Intervention Model: Parallel Assignment, Masking: Double (Participant, Investigator)	Results were not found. Study endpoints are listed below: Safety data including tabulation of AEs, physical exams, vital signs, 12-lead ECGs and clinical lab results PK parameters of ALS-008176 and metabolites in plasma following single and double dose administration Urinary excretion and concentrations of ALS-008176 and metabolites after a single oral dose and multiple doses in healthy volunteers in fasted conditions etc.

Oral GS-5806 activity in a RSV challenge study **2014**	RSV Memphis-37b	This is a randomized, double-blind, placebo-controlled study. This study was conducted in separate cohorts, each cohort contains approximately 20 subjects randomized 1:1 to receive either GS-5806 or placebo. Each subject was admitted to the Quarantine Unit, and inoculated with RSV on Day 0 of quarantine. Subjects were treated with IMP (GS-5806 or placebo) once positive for RSV. The IMP was administered once daily for 5 days. Upon completion of dosing, subjects were observed until Day 12 of quarantine and discharged from quarantine.	Of the 54 participants in cohorts 1 - 4, active treatment was associated with a lower viral load, lower total mucus weight, and a lower AUC for the change from baseline in symptom scores. The results were similar in cohorts 5, 6, and 7. Adverse events, including low neutrophil counts and increased levels of alanine aminotransferase, were more common among participants receiving GS-5806.
The Development of a Human Model of Respiratory Syncytial Virus Infection (protocol) **2016**	RSV-A Memphis 37	Participants will include 30-40 healthy adults age 18-55 years. Study procedures will include brief medical exams, breathing tests, a diary of symptoms, blood tests, samples of fluid (lavage) and cells from the nose, throat and lungs. All participants will receive the virus via drops in the nose. The duration of the study for all subjects will be 6 weeks.	The host response to RSV challenge will be assessed daily for 14 days using methods such as symptom diaries, volume of nasal secretions, numbers of inflammatory cells in nasal mucus, and levels of chemical mediators in nasal fluids. This will be compared with that at baseline and at 28 days post challenge.
Activity of Oral ALS-008176 in a RSV Challenge Study. **2015**	RSV-A Memphis-37b	We conducted a randomized, double-blind, clinical trial in healthy adults inoculated with RSV. Participants received the oral nucleoside analogue ALS-008176 or placebo 12 hours after confirmation of RSV infection or 6 days after inoculation.	A total of 62 participants received placebo or one of three ALS-008176 dosing regimens: 1 loading dose of 750 mg followed by 9 maintenance doses of 500 mg (group 1), 1 loading dose of 750 mg followed by 9 maintenance doses of 150

		Treatment was administered every 12 hours for 5 days. Viral load, disease severity, resistance, and safety were measured throughout the 28-day study period, with measurement beginning before inoculation. The primary end point was the area under the curve (AUC) for viral load, which was assessed immediately before administration of the first dose through the 12th day after inoculation in participants infected with RSV.	mg (group 2), or 10 doses of 375 mg (group 3). In the 35 infected participants, the AUCs for viral load for groups 1, 2, and 3 and the placebo group were 59.9, 73.7, 133.4, and 500.9 log10 PFUs x hours/ml. The time to non-detectability on PCR assay ($P<0.001$), the peak viral load ($P\leq0.001$), the AUC for symptom score ($P<0.05$), and the AUC for mucus weight were lower in all groups receiving ALS-008176 than in the placebo group. Antiviral activity was greatest in the two groups that received a loading dose--viral clearance was accelerated ($P\leq0.05$), and the AUC for viral load decreased by 85 - 88% as compared with the placebo group. Within this small trial, no viral rebound or resistance was identified. There were no serious AEs, and there was no need for premature discontinuation of the study drug.
Safety, Efficacy and PK of BTA-C585 in a RSV Viral Challenge Study (protocol) **2016**	RSV-A Memphis 37b	A Randomised, Phase 2a, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Antiviral Activity Against Respiratory Syncytial Virus Infection, and the Pharmacokinetics of Multiple Oral Doses of BTA-C585 in the Virus Challenge Model Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider,	Results were not found. Study endpoints are listed below: AUC viral load of RSV-A Memphis 37b [Days 2-13] AUC of total RSV symptom scores [Days 1-13] Number of AEs [Screening to Day 28]

		Investigator, Outcomes Assessor)	
An Exploratory Study to Evaluate the Prophylactic Efficacy of a Single Immunization of Ad26.RSV.preF Against RSV Infection in a Virus Challenge Model in Healthy Adults (protocol) **2018**	RSV-A Memphis 37b	An Exploratory, Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Prophylactic Efficacy of a Single Immunization of Ad26.RSV.preF Against Respiratory Syncytial Virus Infection in a Virus Challenge Model in Healthy 18 to 50 Year-Old Adults Intervention Model: Parallel Assignment Masking: Double (Participant, Investigator)	Results were not found. Study endpoints are listed below: VL-AUC for RSV-A Memphis 37b will be determined by qRT-PCR assay of nasal wash samples. The VL-AUC is calculated based on the viral load values measured 2x daily, starting with the baseline value, and ending with the last available value before discharge.
Antiviral Activity of Oral JNJ-53718678 in Healthy Adult Volunteers Challenged With RSV: A Placebo-Controlled Study. **2018**	RSV-A Memphis 37b	After confirmation of RSV infection or 5 days after inoculation with RSV, quarantined participants (n = 69) were randomized to JNJ-53718678 75 mg (n = 15), 200 mg (n = 17), 500 mg (n = 18), or placebo (n = 17) orally once daily for 7 days. Antiviral effects were evaluated by assessing RSV RNA viral load AUC from baseline (before the first dose) until discharge, time-to-peak VL, duration of viral shedding, clinical symptoms, and quantity of nasal secretions.	Mean viral load AUC was lower for individuals treated with different doses of JNJ-53718678 versus placebo. Also, mean peak VL, time to peak VL, duration of viral shedding, mean overall symptom score, and nasal secretion weight were lower in each JNJ-53718678-treated group vs. placebo. No clear exposure-response relationship was observed. Three participants left due to treatment-emergent AEs of grade 2 and 1 electrocardiogram change and grade 2 urticaria (placebo).
A Study of PC786 to Evaluate the Antiviral Activity, Safety and Pharmacokinetics of Multiple Doses in an RSV Challenge Study (protocol)	RSV	A Single-blind, Placebo Controlled, Randomised Study to Evaluate Antiviral Activity and Safety and Pharmacokinetics of Inhaled PC786 Against Respiratory Syncytial Virus (RSV) in Healthy Adult Subjects in a Virus Challenge Model	Results were not found. Study endpoints are listed below: RSV viral load [Baseline to Day 28] AUC 0-t for RSV viral load measured in nasal washes by reverse transcription quantitative PCR (RT-qPCR)

2018			
RSV-A dynamics and the effects of lumicitabine, a nucleoside viral replication inhibitor, in experimentally infected humans. **2019**	RSV-A Memphis-37b	This challenge study was a randomized, double blind, placebo-controlled, multiple-dose study to evaluate the efficacy of lumicitabine in RSV-infected healthy adult subjects. The study enrolled 62 healthy adults, consisting of placebo (n = 18) and lumicitabine treatment subjects (n = 44). Patients were inoculated with RSV while under quarantine. Each subject received 1 mL of the inoculum (104 pfu) INly on day 0. Infected patients were randomly assigned placebo or lumicitabine group. The single oral loading dose and maintenance dosing regimens of lumicitabine were 750 mg LD then 150 mg q12h; 375 mg q12h (no LD); or 750 mg LD then 500 mg q12h. Subjects received lumicitabine treatment for 5 days.	A semi-physiological model was linked to predict ALS-8112 conversion to active intracellular NTP. Extensive and rapid RSV reduction occurred after lumicitabine treatment, with >99% viral inhibition at 2 h after loading dose. Simulated NTP exposures and time to EC50 attainment suggested that rapid therapeutic effects and reduced dosing frequency are achievable in adult and paediatric patients. The semi-mechanistic model characterizes RSV kinetics and the antiviral effectiveness of lumicitabine in an adult challenge population. This model is applicable to guide dose selection in adult and paediatric patients.
A Randomized, Double-blind, Placebo-controlled, First-in-human, 6-Part Study of Orally Administered JNJ-64417184 ... in healthy subjects (protocol) **2019**	RSV-A Memphis-37b	This is a randomized, double-blind, placebo-controlled, first-in-human, 6-Part Study of orally administered JNJ-64417184 to evaluate the safety, tolerability, and pharmacokinetics of single and multiple ascending doses, and the antiviral activity of multiple doses in a RSV challenge study in healthy subjects. Intervention Model: Sequential Assignment	Results were not found. Study endpoints are listed below: Number of Participants With Adverse Events (AEs) as a Measure of Safety and Tolerability, Laboratory Abnormalities, clinically Significant Changes in Vital Signs... Area Under the Concentration-Time Curve Between Time of First Administration and Dosing Day 7

		Masking: Double (Participant, Investigator)	
A Study to Explore the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and PKs of JNJ-53718678 at 2 Dose Levels in Non-Hospitalized Adult Participants Infected With RSV (protocol) **2019**	RSV strain unspecified	A Pilot Phase 2a, Randomized, Double-blind, Placebo-controlled study to explore the antiviral activity, clinical outcomes, safety, tolerability, and pharmacokinetics of JNJ-53718678 at 2 dose levels in non-hospitalized adult subjects infected with RSV. The study will examine 2 dose levels (80 mg and 500 mg) daily for 7 days in adults with RSV infection as measured by RSV viral load in nasal secretions by qRT-PCR assay.	Results were not found. Study endpoints are listed below: Area Under the Viral Load-time Curve, Viral load AUC will be determined by qRT-PCR assay of nasal swabs. RSV viral load over time will be measured by qRT-PCR assay in the mid-turbinate nasal swab specimens. Change from baseline in RSV viral load over time will be measured by qRT-PCR assay in the mid-turbinate nasal swab specimens. Time (hours) to un-detectable RSV viral load
A Phase 2a Study to Evaluate EDP-938 in the Virus Challenge Model (protocol) **2019**	RSV-A Memphis 37b	A randomised, Phase 2a, double-blind, placebo-controlled study to evaluate the safety, pharmacokinetics and antiviral activity of multiple doses of orally administered EDP-938 in healthy subjects infected with RSV-A Memphis 37b. This study is designed to compare the antiviral effect of EDP-938 compared to a placebo control in the respiratory syncytial virus challenge model. Intervention Model: Parallel Assignment, Masking: Double (Participant, Investigator)	Results were not found. Study endpoints are listed below: Area under the curve for RSV viral load as measured by RT-qPCR assay from the first viral load measurement post initial dose of EDP-938 or placebo through day 12 Change of baseline symptoms post initial dose of EDP-938 or placebo through Day 12
Epitope-specific airway-resident CD4+ T cell dynamics during experimental human RSV infection.	RSV A Memphis 37	Healthy, non-smoking adults 18-55 years of age were enrolled outside the RSV season, inoculated with 1 × 104 PFUs of RSV A M37 by i.n. drops and quarantined for 10 days. They returned on days	Human infection challenge study identified the specificity and dynamics of RSV-specific T-cell responses in the target organ, allowing the investigation of Trm recognizing novel viral

2020		+14 and +28 for sampling in the convalescence period. An additional 8 volunteers were enrolled subsequently for further phenotypic analysis of RSV-specific CD4+ T cells in blood and the lower airway were analyzed by flow cytometry and immunohistochemistry. Bronchial soluble mediators were measured using quantitative PCR and MesoScale Discovery. Epitope mapping was performed by IFN-γ ELISpot screening, confirmed by in vitro MHC binding.	antigens over time. The new tools that were described enable precise tracking of RSV-specific CD4+ cells, potentially accelerating the development of effective vaccines. No mention of AEs.

Appendix B: Supplementary Materials Phase I Narsyn Results

Example 5

Safety of narsyn was determined through a phase I randomized-controlled trial. Crossover safety study in healthy adult volunteers. After favorable ISC evaluation, study B will start. The objective of this trial was to measure the safety of IN administration of palivizumab in healthy adults. The study population consisted of healthy adult men and women 18-60 years of age. One nose drop in the right nostril once daily of 1 mg/mL palivizumab (narsyn) or placebo for 7 days; 14 day washout period, then crossover to other arm for 7 days. The main study outcome is self-reported symptoms according to the FDA scorecard and SAE's. The phase IIb will be initiated based on the overall safety profile. The study will proceed to study B if no serious adverse events or other AE are considered to be treatment-related by the investigators and the ISC. As there were no treatment-related adverse events and no severe adverse events, the ISC found the safety profile to be acceptable and gave a positive advice to continue on to the phase IIB trial.

Table 11. Airway patency 10 minutes after nasal drop during arm 1 of phase I crossover safety trial in trial participants who received Narsyn or placebo. There was one exclusion in the placebo group (9/10 participants).

Airway Patency After 10 Minutes	Narsyn (n = 10)	Placebo (n = 9)
Patent % (n)	100 (10)	100 (9)

Table 12. Local and general symptoms per participant in the placebo and narsyn trial arms. Symptoms were scored daily during treatment according to a symptom scorecard from 0 to 3. 0: no symptoms; 1: mild, does not hinder daily activities; 2: moderate, hinders daily activities; 3: severe, not able to perform daily activities. If there were no reported symptoms ("0" in diary) then 0 was not reported in this table. D: day (days were numbered from 1 to 7 in each trial arm.

Subject	Placebo			Narsyn		
	Local Symptoms* (Right Nostril)	Local Symptoms* (Left Nostril)	General Symptoms*	Local Symptoms* (Right Nostril)	Local Symptoms* (Left Nostril)	General Symptoms*
1			D2-4: headache 1	D2: Itchy nose 1 D2&4: Runny nose 1		D6: headache 1
2						
3						
4						
5						

6						
7						
8				D6-7: Stuffy nose 1		
9				D3-4 Runny nose 1	D3-4 Runny nose 1 D4: Itchy nose 1	D3-5 Sneezing 1
10						
11						D2: Headache 1
12	EXCLUSION					
13	D6-7: Runny nose 1 D7: Stuffy nose 1		D6-7: Sneezing 1			D2: Sneezing 1
14						
15						
16						
17	D1-5 Stuffy nose 1	D1-5 Stuffy nose 1		D3-7 Stuffy nose 1 D3-7 Runny nose 1	D3-7 Stuffy nose 1 D3-7 Runny nose 1	D2,6,7 Sore throat 1 D3-5 Sore throat 2 D3-7 Sneezing 1 D3-5 Fatigue 1 D5 Headache 1
18						
19						Vague feeling in right ear
20			D4: Sore throat 2			During use sometimes felt right nostril less open, with no use this was less. No relation with moment of administration

Table 13. Composite severe adverse events in either trial arm. *As determined by ISC. SAE: severe adverse event. AE: adverse event, ISC: data safety monitoring board

	Placebo (n=19)	Narsyn (n=19)
SAE's % (n)	0 (0)	0 (0)
AE's % (n)	4 (21.1)	6 (31.6)
Objectifiable treatment-related AE's*	0 (0)	0 (0)

Table 14. Overview of adverse events from both trial arms including conclusion about whether or not adverse event was treatment-related. NA: not applicable.

Intervention	Symptom	Home visit	Nasal Swab PCR	Conclusion
Placebo	Mild headache day 2-4	Not done because not objectifiable symptoms	NA	Not treatment-related
Narsyn	Mild itchy nose right day 2 Mild runny nose right day 2 and 4 No symptoms on day 3 Mild headache day 6	Not done because subject did not inform study team	NA	Not treatment-related
Narsyn	Mild stuffy nose right day 6-7 Stuffy nose alternated open/closed left/right	Stuffy nose right; no stuffy nose left Hoarse voice 2 children had a cold before subject became sick	Rhinovirus	Viral infection, not treatment-related
Narsyn	Runny nose left day 3 & 4 Runny nose right day 3 & 4 Itchy nose left day 4 Sneezing day 3, 4, 5	Not objectified because subject only contacted study team for left-sided symptoms	Negative	Not treatment-related
Narsyn	Mild headache day 2	Not done because not	NA	Not treatment-related

	"Short migraine, I have this symptom more often"	objectifiable symptom		
Narsyn	Mild sneezing day 2 Duration of symptoms <1 day	Not done because patient did not inform study team	NA	Not treatment-related
Placebo	Mild runny nose right day 6-7 Mild stuffy nose right day 7 Sneezing day 6-7	Symptoms not objectifiable during home visit Left and right nostrils patent No runny nose, no sneezing Son had a cold before subject	Rhinovirus	Viral infection, not treatment-related
Narsyn	Mild stuffy and runny nose right day 3-7 Mild stuffy and runny nose left day 3-7 Sore throat mild day 2,6, 7; moderate day 3-5 Mild sneezing day 3-7 Mild fatigue day 3-5 Mild headache day 3	Not done because symptoms bilateral	Parainfluenza	Viral infection, not treatment-related
Placebo	Mild stuffy right day 1-5 Mild stuffy nose left day 1-5	Not done because subject didn't notify study team, continuation of cold symptoms week 1	NA	Not treatment-related
Placebo	Moderate sore throat day 4	Not done because	NA	Not treatment-related

		symptoms not-objectifiable		

Appendix C: Supplementary Material: Challenge Virus Handling

Source and Safety Testing

The RSV stock intended for use in this study is designated RSV Memphis 37 and is supplied by Imperial College London. The virus was isolated from a child with severe RSV infection in the US in 2007 and manufactured according to current Good Manufacturing Practice (cGMP) in human vero cells.

RSV Memphis 37 is produced by expanding the plaque purified virus through 5 passages in clinical grade qualified Vero cells (WHO 10-87) in Meridian Life Science's cGMP biomanufacturing suite. This process was conducted according to current cGMP as defined in Title 21 of the United States Code of Federal Regulations, Parts 210 and 211, as applicable to the manufacture of Phase I clinical trial material(s). The material was then tested according to the appropriate ICH and FDA guidance documents for the production of a human clinical vaccine product. Briefly, the identity of the inoculating virus (RSV) was confirmed by an immunofluorescent antibody assay, electron microscopy, and N-gene sequencing. It was determined at several steps in the selection and manufacturing process to be free of adventitial agents and human pathogens by four methodologies: 1) twenty-eight day culturing in 5 indicator cell lines (MRC-5, Vero, MDBK, HeLa, MEF) while under specific RSV neutralization conditions (high concentrations of RSV-specific monoclonal antibody). Routine cytopathic effect observations, hemabsorption and hemagglutination at 14 days were performed, followed by blind passage and identical repeat evaluations after an additional 14 days (Bioreliance Inc. Rockville MD, USA). 2) Product-enhanced reverse transcriptase assay for the general detection of retrovirus reverse transcriptase (Bioreliance Inc. Rockville MD, USA); 3) an expansive series of individual PCR assays designed to detect human pathogens; 4) electron microscopy. The Memphis 37 virus preparation is presented in 1mL vials diluted in DMEM and 25% sucrose.

Storage of Inoculum

The inocula will be stored at the department of Pediatric Immunology. Vials of inoculum are not opened until ready for dilution on the day of inoculation into the patient.

The inocula do not have a definite shelf-life, but are expected to maintain infectivity in the majority of subjects, and are expected to have almost indefinite shelf life at the storage temperature of -80°C (REF: Stabilization of respiratory syncytial virus (RSV) against thermal inactivation and freeze-thaw cycles for development and control of RSV vaccines and immune globulin. Vaccine 14, 1417-1420 (1996))

Diluted Inoculum

RSV A Memphis 37 is presented in 1mL vials diluted in 25% sucrose and DMEM. The titer of the virus is given as $3x10^6$ pFU/mL by plaque assay in Vero cells by the manufacturers. This is equivalent to ~16000 (4.2 log) pFU/mL by plaque assay in HEp-2 cells (DeVincenzo J, personal communication). The titer of the virus stock stored at Imperial College must be determined prior to the start of any infection study, as virus stock may degrade over time. This will be performed using standard plaque assay in HEp-2 cells.

Previous studies in healthy adults have used 4-5 log $TCID_{50}$ per subject or 3-5 log pFU, depending on virus strain. Doses are given by the IN route as drops (0.5mL per nares). Doses in this range appear to have a consistent infection rate of 50-80% in all subjects; those with lower serum RSV microneutralization titers (<9.36 log2) appear more susceptible. (REF: Lee, F.E., Walsh, E.E., Falsey, A.R., Betts, R.F. & Treanor, J.J. Experimental infection of humans with A2 respiratory syncytial virus. Antiviral Res 63, 191-196 (2004))

RSV A Memphis 37 should not normally be diluted prior to inoculation. If a lower dose than 4.2 log pFU is required, then this can be achieved by using a smaller volume of undiluted virus. If multiple subjects are to be inoculated on the same day, multiple vials should be opened and the contents mixed together on ice in a Class II Biosafety cabinet to eliminate batch variability.

Once inocula are prepared they must be kept on ice and administered to subjects within 1 hour to avoid degradation. Thawed or mixed inocula must not be stored or refrozen, as this will result in inactivation. Any concentrated inoculum vial that has been opened and thawed for preparing dilute inocula, and that is surplus to requirements must be inactivated and discarded and not re-sealed and administered to volunteers.

Transport of inocula to UMCU

Labelled inocula are stored at -80°C in the designated laboratory of the UMCU in the WKZ. Inocula are transported to the UMCU in their original sealed vials, with labelling on the vial and/or transportation vessel to include the clear designation:
"**Respiratory syncytial virus: Live Virus Inoculum**".

Inocula will be placed on ordinary ice within a closed polystyrene box.

Inocula will not be opened until in the designated room of the WKZ in which volunteers are to be inoculated.

Disposal

Disposal of any unused Challenge Virus inoculum vials will be in accordance with RVL's SOPs.

Supply and accountability

Accurate records of receipt and condition of all Challenge Virus stock will be available for verification by the Study Monitor. Trained clinical site staff will be responsible for adequate and accurate accounting of all Challenge Virus inoculum and other materials used and unused. Any departures from the protocol-dispensing regimen will be fully documented.

Appendix D: Clinical symptom score diary cards of the upper respiratory tract

	Day											
Symptom	1	2	3	4	5	6	7	8	9	10	11	12
Sneezing												
Headache												
Malaise												
Fever / chills												
Nasal discharge												
Nasal obstruction												
Sore throat												
Cough												
Total score												

Absent = 0 Mild = 1 Moderate = 2 Severe = 3

Definition of a clinical cold

A clinical cold is diagnosed if **two or more** of the following are present:

- A cumulative clinical symptom score of 14 or greater over a 6 day period
- Nasal discharge is present on three or more days over the six-day period post viral inoculation
- A subjective impression of a cold developing. This latter criterion is used because there are a few subjects who have had a very strong subjective impression of a clinical cold but the cumulative clinical score does not reach the arbitrary cut-off level

Clinical symptom score diary cards of the lower respiratory tract

	Day											
Symptom	1	2	3	4	5	6	7	8	9	10	11	12
Cough on waking												
Wheeze on waking												
Daytime cough												
Daytime wheeze												
Daytime shortness of breath (SOB)												
Nocturnal cough, wheeze, or SOB												
Total score												

Absent = 0 Mild = 1 Moderate = 2 Severe = 3

Appendix E: Research concerning RSV transmission modes and prevention measures

Winther et al., Journal of Medical Virology, 2007

This study was designed to assess rhinovirus contamination of surfaces by adults with colds, and it observed the transfer of rhinovirus from surfaces to fingertips during normal daily activities. Fifteen adults with natural rhinovirus colds stayed overnight in a local hotel. Ten adults touched sites in each room were tested for rhinovirus RNA using RT-PCR. Door handles (7/14) and pens (6/14) were the most frequently contaminated sites followed by light switches, TV remote controls, and faucets (each 6/15), and tele- phones (5/15) (Table I).

Hall et al., *The Yale Journal of Biology & Medicine*, 1982

This study examined the survival of RSV in fresh secretions on various surfaces surrounding an infected infant's bed. Results showed that RSV's extracorporeal survival and infectivity varied with the type of surface it was on, environmental humidity, and the temperature. RSV could survive for 6-12 hours on non-porous surfaces, such as plastic and counter tops. RSV could reach these surfaces by transfer from an infected individual's hands.

Hall et al., *Brief Clinical and Laboratory Observations*, 1981

In this study, adult volunteers were exposed in one of three ways to infected babies admitted with RSV lower respiratory tract infection. The first group, called "cuddlers," were exposed by caring for an infant in the usual manner, such as feeding, changing, and playing with the baby. These caretakers wore gowns on direct contact, but no masks. The second group, called "touchers," were exposed by touching various objects and surfaces about the infant's bed and then touching their eyes or nose at a time when the infected infant was out of the room. The third group, called "sitters," were exposed by sitting at a distance of greater than six feet from an infected infant. The sitters were gowned, gloved, and could read but were not allowed to touch anything. Hence cuddlers could be exposed by any of the three. Possible modes of transmission- large-particle aerosols, self-inoculation after touching fomites, and small-particle aerosols. Touchers, on the other hand, would be exposed only by self-inoculation from touching contaminated surfaces. Sitters would be infected only by small-particle aerosols. Cuddlers and touchers became infected, but none of the sitters. This suggests that RSV may be spread by close contact with direct inoculation of large-particle aerosols or by self-inoculation after touching contaminated surfaces. However, spread by small-particle aerosols does not seem to be a major mode of transmission.

Hall et al., *Infection and Immunity*, 1981

In 1981 longstanding RSV researcher, Caroline Hall, inoculated 32 young adult volunteers with RSV o understand the efficiency of transmission via different routes. RSV was administered by nose (n=4), by eye (n=4) and by mouth (n=8). In the highest viral inoculation dose infections occurred most efficiently by nose and eye but not by mouth; serving as evidence that intranasal and ocular inoculation are potential routes of infection. **However, the mouth appears to be an insensitive route of inoculation.**

Appendix F Letter of Support/ Assessment of Feasibility from RSV-PAB

Aan: Wilhelmina Kinderziekenhuis

t.a.v.: RSV onderzoeksgroep, N. Mazur

Postbus 85090

3508 AB Utrecht

Datum: 28 augustus 2020

Betreft: Onderzoeksvoorstel: De deurwachter hypothese: intranasale toediening van palivizumab om respiratoir syncytieel virus (RSV) infectie te voorkomen.

Geachte mevrouw Mazur,

U heeft ons - Parent Advisory Board (PAB) van de RSV Onderzoeksgroep van het WKZ - gevraagd uw onderzoeksvoorstel te beoordelen vanuit patiëntenperspectief. Omdat de PAB-leden tot de groep van potentiële studiedeelnemers behoren, heeft u ons specifiek gevraagd een inschatting te maken van de haalbaarheid van de voorgestelde studieopzet in relatie tot de werving van deelnemers.

Als ouders van kinderen die (soms ernstig) ziek zijn geweest van een RSV-infectie, hebben wij de mogelijke impact van RSV van dichtbij ervaren. Met uw onderzoek kan een belangrijke stap worden gezet richting het beschikbaar komen van een betaalbaar, acceptabel en effectief middel ter voorkoming van ernstige RSV-infecties bij baby's. Wij onderstrepen dan ook het grote potentiële belang van de studie.

Ons oordeel over de haalbaarheid van de studieopzet is gebaseerd op een inschatting van de risico's en belasting voor de deelnemers en luidt als volgt.

Wij achten de risico's voor studiedeelnemers beperkt. Het is onwaarschijnlijk dat de experimentele RSV-infectie bij de deelnemers tot ernstige gezondheidsklachten zal leiden of dat zij ernstige bijwerkingen zullen ondervinden van palivizumab. Omdat deelnemers voor dit onderzoek in quarantaine gaan, is ook het risico op transmissie van de RSV-infectie naar niet-deelnemers minimaal.

De belasting van deelnemers tijdens de uitvoering van het onderzoek is op zich ook beperkt en achten wij acceptabel. Wij verwachten echter wel dat de quarantaineperiode door potentiële deelnemers als belastend wordt gezien en een belangrijke praktische drempel zou kunnen zijn voor deelname.

Wij adviseren u om bij de uitwerking van beide studieonderdelen de impact van de quarantaineperiode op het dagelijks leven van de deelnemers en hun gezinnen zo veel mogelijk te minimaliseren. Zorgvuldige voorbereiding en communicatie over de praktische implicaties van deelname zal de deelnamebereid en daarmee de haalbaarheid van de studieopzet vergroten.

Aangezien u deelnemers geen vergoeding volgens het wage-payment model kunt bieden is het van belang zij een intrinsieke motivatie hebben om mee te doen. Het werven van deelnemers onder ouders van kinderen die aan eerdere klinische RSV-onderzoeken hebben meegewerkt, is daarmee een logische strategie.

Het werven van deelnemers zal wellicht een uitdaging zijn, maar is ons inziens zeker niet onhaalbaar.

De PAB is al vanaf het begin betrokken bij uw project en zal ook in toekomstige onderzoeksfases actief betrokken blijven en waar mogelijk bijdragen aan het behalen van onderzoeksresultaten. Wij ondersteunen het voorgestelde onderzoek en uw beursaanvraag bij het Longfonds dan ook van harte.

Met vriendelijke groet,

mede namens de andere PAB-leden,

Nicole Derksen-Lazet

Parent Advisory Board van de RSV Onderzoeksgroep WKZ