Implementing a new controlled human infection model with a novel Respiratory Syncytial Virus (RS virus) in healthy volunteers.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Viral infectious disorders
Study type	Interventional research applied for the first time in human subjects

Summary

ID

NL-OMON57515

Source
Onderzoeksportaal

Brief title
INNO4VAC RSV CHIM validation study

Condition

- Viral infectious disorders

Synonym
RSV infection

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research

Source(s) of monetary or material Support: Europese Unie

Intervention

- Other intervention

Explanation

N.a.

Outcome measures

Primary outcome

To establish a controlled human infection model for RSV-B for future drug and vaccine testing
To investigate the safety and tolerability of controlled infection after inoculation with the GMP-produced wild-type RSV-B strain
To identify the inoculation dose of a new, GMP-produced wild-type RSV-B strain, needed to induce RSV infection and with a new strain in 50-70% of exposed healthy adult volunteers

Secondary outcome

To assess the RSV shedding kinetics in nasal swab
To characterize RSV disease after inoculation with a GMP-produced wild-type RSV-B strain
To evaluate the systemic and mucosal immune response

Study description

Background summary

Respiratory syncytial virus (RSV) infections of the upper and lower respiratory tract are a leading cause of morbidity and mortality in infants, elderly, and immunocompromised patients. Although RSV vaccine development has been conducted since the 1960s, only recently the first RSV vaccines have become available. While the currently available vaccines have shown positive results in phase III trials, it remains unclear how effective they will be in terms of durability of protection, transmission reduction, large-scale production and world-wide access.

To accelerate the product development pipeline and select potential compounds and vaccines early in clinical development before being tested in vulnerable populations, we aim to establish a novel controlled infection model for human RSV, using a recently developed, good manufacturing practice (GMP)-produced, RSV-B strain. Since all currently available RSV challenge agents are derived from A-type strains circulating in 2015 or earlier, this will be the

only RSV-B challenge virus that contains the genotypic duplications that characterize all contemporary circulating variants.1,2 This RSV strain is from a recent clinical isolate (2023) and prepared with a minimum number of passages to avoid cell line adaptations. The virus stock is fully characterized and tested for all related quality and safety controls required for a pharmaceutical viral product meant for intranasal application in humans.

In this study, we aim to establish a CHIM using a GMP-produced RSV-B strain for future drug and vaccine testing and to identify the inoculation dose needed to induce RSV infection with this new strain in approximately 50-70% of exposed healthy adult volunteers. In concordance with recent developments in regulatory considerations concerning RSV CHIMs, we aim to conduct this RSV CHIM in an outpatient setting.

Study objective

The main objective of the study is to establish a controlled human infection model (CHIM) for RSV for future drug and vaccine testing and to identify the inoculation dose needed to induce RSV infection with this new strain in 50-70% of exposed healthy adult volunteers in that dose group. Also, we will investigate the safety and tolerability of the inoculum by assessing the nature, frequency, and severity of adverse events. Furthermore, self-reported symptom scores, RSV shedding kinetics in nasal swab and immune (humoral and cellular) responses will be investigated during the controlled experimental RSV infection.

Study design

The trial will be an open label, adaptive dose-escalating intervention study. The study consists of three main phases: screening/enrollment, inoculation, and follow-up. After eligibility assessment at screening, healthy adult subjects will be included in the study; a maximum of 30 subjects will be included in total. After the pilot group (n=3) of each cohort has been inoculated, predetermined go/no-go criteria based on safety data and infection rate will determine whether the next group receives the same or a higher inoculation dose. The next cohort will either be dosed with a 10-fold higher dose (n=3) or will be inoculated with the same dose (n=7, confirmatory group) within the same cohort. After inoculation of the confirmatory group, the safety, infection rate and additional data on viral kinetics and disease characteristics are assessed again, to determine whether the remaining of the in total 30 subjects will receive the same or a higher dose of the challenge virus.

This RSV CHIM will be conducted in an outpatient setting; subjects will attend study activities on the days indicated in Table 1. Subjects will complete daily symptom questionnaires at home, either on paper or digitally (ePro). After inoculation with the virus, isolation measures will apply when participants develop symptoms of respiratory infection. A thorough rationale supporting this can be found in the structured risk analysis in Section 10.

During visits, subjects will be monitored for solicited and unsolicited adverse events (AE) and vital signs including tympanic temperature. Solicited symptoms will be the symptoms addressed by the modified Jackson score and the WURSS-24 questionnaire, including nasal congestion, rhinorrhea (runny nose), sore throat, itchy/irritation of the eyes, wheezing/dyspnea, coughing, malaise (feeling sick), sneezing, myalgia/arthralgia, headache,

earache, and fever. If any of the symptoms addressed by the questionnaires are reported as severe by the participant or classified as severe by the investigator, or if they last longer than 14 days, they will be recorded as AE.

Routine safety laboratory assessments (blood chemistry and haematology) will be performed; additional safety laboratory assessments will be performed if deemed necessary by the investigator. Before and after the challenge, nasal and serum specimens and peripheral blood mononuclear cells (PBMCs) will be collected for virology and immunological analysis. For timing of assessments, see Table 1. If subjects remain PCR positive for the inoculated strain on day 11 post-inoculation, at the discretion of the physician, the subjects are to return to the center for a PCR test on day 12 post-inoculation. If by day 12 subjects still show a positive PCR result, the PCR status will be followed up at the discretion of the investigator. All subjects will return to CHDR for follow-up visits on days 15, 29 and 90 post-inoculation.

Intervention

Volunteer groups will be inoculated intranasally with escalating doses of the GMP-produced wild-type RSV-B-I54 strain, that was isolated in a male pediatric patient patient of 21 months old, admitted to the Utrecht University Medical Centre (UMCU) hospital in 2022, with parental consent obtained. The virus is produced according to good manufacturing practices (GMP) at Naobios Biomanufacturing Services, Saint-Herblain, France. The starting dose is 1 x 104 TCID50 in 1 mL, divided between both nostrils. Inoculation will be performed by intranasal administration of droplets according to CHDR SOP CGEVIRIN. Doses will be escalated by 10-fold steps for every dose group.

Study burden and risks

The risk associated with the administration of RSV B-I54 to humans have not been identified as this strain has not yet been administered to humans before. All volunteers participating in the study are at risk of developing RSV symptoms. They may develop any of the common cold symptoms such as sore throat, nasal congestion, rhinorrhea, sneezing, coughing, fatigue and fever. However, due to the nature of this type of virus and the fact that all adults will have prior immunity from multiple previous exposures to RSV, the clinical symptoms are expected to be mild and of moderate duration. RSV challenge strains have been administered before to humans and have been shown to be safe.23 Volunteers may experience discomfort during the collection of blood and nasal samples. However, the potential risk of venipuncture for blood sampling is mild and is considered low. The major benefit of this study is in developing a novel controlled human infection model using a contemporary RSV strain, which will enable us to evaluate the efficacy of interventions against RSV efficiently and early in the clinical development.

Contacts

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Trial sites

Trial sites in the Netherlands

Centre for Human Drug Research (CHDR)
Target size: 30

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Age 18-55 years at screening;

2. A total body weight ≥50 kg and body mass index (BMI) ≥18.0 and ≤32.0 kg/m2;

3. Good health, based upon the results of medical history, physical examination, vital signs, ECG, and laboratory profiles of both blood and urine, as determined by the investigator;

4. Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby;

5. Subject is able to communicate well with the investigator, and is willing to adhere to study procedures and measures regarding self-isolation;

6. The following inclusion criteria are applicable to subjects undergoing viral challenge who are in a sexual relationship:

a. Female subjects must have a negative pregnancy test at screening and just prior to the date of viral challenge;

b. Female subjects of childbearing potential must be using contraception consisting of an acceptable form of birth control starting from at least 2 weeks prior virus inoculation and continuing throughout the study duration (until Day 90);

c. Female subjects who are not of childbearing potential;

7. Subject has signed informed consent form prior to any study procedures.

Exclusion criteria

1. Prior inoculation with a virus from the same virus family (Pneumoviridiae) as the challenge virus;

2. Prior participation in another controlled human infection study with a respiratory virus in the preceding 6 months taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study;

3. Share household, work closely or have close contact with infants (<4 years of age), pregnant women, immune-compromised and/or clinically vulnerable elderly (≥65 years old) individuals for 30 days after RSV inoculation;

4. Any history of physician-diagnosed and/or objective test-confirmed asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, or chronic lung condition of any aetiology. A history of childhood asthma without respiratory disease in adulthood may be accepted;

5. Nasopharyngeal swab indicative for Influenza or other respiratory virus infection, including asymptomatic positive PCR test for SARS-CoV-2, determined by PCR at baseline visit (day -1);

6. Upper or lower respiratory tract infection or febrile illness (temperature ≥37,9°C), in the period of 4 weeks before virus inoculation;

7. Receipt of any vaccine within 28 days prior virus inoculation or during the study period, until the last follow-up visit (Day 90); receipt of an RSV vaccine at any time or planned RSV vaccination in the 3 months following virus inoculation;

8. Females who are breastfeeding, or have been pregnant within 6 months prior to the study, or have a positive pregnancy test at any point during screening or prior to viral challenge, or

are planning to become pregnant during the study;

9. Any confirmed or suspected disease or condition associated with immune system impairment, including auto-immune diseases, HIV, asplenia or recurrent severe infections;

10. Prior use or planned receipt of immunosuppressive medication (systemic and intranasal glucocorticoids six months prior to inclusion or any other systemic immunosuppressive medication at any time), immunoglobulins or systemic antiviral therapy;

11. Symptoms of active hay fever or other allergies that involve the airways, during screening or prior to inoculation;

12. Any known history of anaphylaxis or any significant allergy against the excipients of the virus challenge inoculum (sucrose, phosphate-buffered saline);

13. Any anatomic or neurologic abnormality impairing the gag reflex, or associated with an increased risk of aspiration, or any abnormality significantly altering the anatomy of the nose or nasopharynx in a substantial way that may interfere with the aims of the study and in particular any of the nasal assessments or viral challenge;

14. History of frequent epistaxis (nose bleeds) in the six months prior to inoculation and/or history of being hospitalized due to epistaxis on any previous occasion;

15. Any nasal or sinus surgery within 3 months of the date of viral challenge;

16. Smokers or ex-smokers with more or equal to 5 pack years smoking history.

17. Any smoking in the 30 days preceding screening, including e-cigarettes;

18. History of abuse of addictive substances (alcohol, illegal substances) or current use of more than 21 units alcohol per week, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent;

19. Positive test for illicit drug use at screening or prior to inoculation (with the possibility of a retest);

20. Participation in an investigational drug or device study within 3 months prior to inoculation or more than 4 times a year;

21. Loss or donation of blood over 500 mL within three months (males) or four months (females), or plasma within 2 weeks prior to screening or intention to donate blood or blood products during the study;

22. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including blood biochemistry, hematology and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before inclusion to confirm eligibility or judged to be clinically insignificant;

23. Receipt of blood or blood derived products within 180 days prior to virus inoculation;

24. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening;

25. Any history or evidence of any clinically significant or currently active cardiovascular, respiratory, dermatological, gastrointestinal, endocrinological, hematological, hepatic, immunological (including immune suppression), metabolic, urological, renal, neurological or psychiatric disease, and/or other major disease, or condition, including a history of malignancy, that, in the opinion of the investigator, may interfere with a subject completing the study and the necessary investigations (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, and body temperature) and ECG). Minor deviations from the normal range may be accepted, if judged by the Investigator to have no clinical relevance.

26. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results, as deemed by the investigator.

Study design

Design

Study phase:	N/A
Study type:	Interventional research applied for the first time in human subjects
Intervention model:	Single
Allocation:	N/A: single arm study
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-05-2025
Enrollment:	30
Duration:	5 months (per patient)
Type:	Actual

Medical products/devices used

Product type:	N.a.

IPD sharing statement

Plan to share IPD: Undecided

Plan description
N.a.

Ethics review

Approved WMO Date:	25-04-2025
Application type:	First submission
Review commission:	METC LDD
Approved WMO Date:	10-06-2025
Application type:	Amendment
Review commission:	METC LDD

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Research portal	NL-009168