A Dose-Finding and Longitudinal Biomarker Study of Rhinovirus Challenge in Healthy Volunteers and Mild-Moderate Asthmatics to Evaluate the Safety and Use of a Human Rhinovirus Preparation in Developing High Dimensionality Phenotypes (*Handprints*) for Asthma

Published: 16-10-2013
Last updated: 22-04-2024

The overarching goal is to qualify a virus challenge model for use in basic research and clinical development. This model will provide a consistent approach to generating and testing hypotheses relating to virally induced asthma exacerbations, and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON41599

Source
ToetsingOnline

Brief title
MK0000-218

Condition

- Bronchial disorders (excl neoplasms)

Synonym
asthma, dyspnea, respiratory disease

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Europese Unie,Merck

Intervention

Keyword: Asthma, Challenge, Rhinovirus

Outcome measures

Primary outcome

Study Part 1

(1) Objective: To establish the safety and tolerability of nasal challenge with RV16UB in healthy subjects.

Hypothesis: In healthy subjects, single nasal challenge with RV16UB is sufficiently safe and well tolerated to permit its evaluation in asthmatic subjects.

(2) Objective: To establish the safety and tolerability of nasal challenge with RV16UB in mild to moderate asthmatics on inhaled corticosteroids (ICS).

Hypothesis: In mild to moderate asthmatics taking ICS, single nasal challenge with RV16UB is sufficiently safe and well tolerated to permit its use in Part 2.

(3) Objective: To select a dose of RV16UB that induces symptoms at days 1-7 in most asthmatics following nasal challenge

Hypothesis: At least one of the four challenge doses of RV16UB will be associated with

a) significant elevation above baseline of mean maximum post-challenge Jackson cold symptom scores (CSS), and

b) at least three (3) members in the dose group having diary-based CSS * 3 for two days in a row, and

c) at least four (4) members in the dose group demonstrating at least 1000 copies /mL of viral RNA in nasal lavage fluid as measured by qRT-PCR.

(4) Objective: To determine whether mild to moderate asthmatics taking LABA are appropriate participants in nasal challenge studies with RV16UB.

Hypothesis:

I) In mild to moderate asthmatics taking ICS and LABA, single nasal challenge with RV16UB is sufficiently safe and well tolerated to permit its use in Part 2.

II) Cohorts of LABA-taking asthmatics demonstrate the similar nasal and viral shedding characteristics as asthmatics not taking LABA.

At least one of the four challenge doses of RV16UB will be associated with the following in a cohort of LABA-taking asthmatics:

a) significant elevation above baseline of mean maximum post-challenge Jackson cold symptom scores (CSS), and

b) at least three (3) members in the dose group having diary-based CSS * 3 for two days in a row, and

c) at least four (4) members in the dose group demonstrating at least 10^3 copies/mL of viral RNA in nasal lavaage fluid as measured by qRT-PCR.

Study Part 2

(1) Objective: To assess the change from baseline (CFB) in time-weighted average (TWA) morning FEV1 on days 1-7 following RV16UB challenge with the dose selected from Part 1.

Hypothesis: The percent CFB in TWA morning FEV1 on days 1-7* after RV16UB infection will be less than zero on average. The mean TWA %CFB is at least -10% (reduction).

(2) Objective: To assess the change from baseline (CFB) in time-weighted average (TWA) evening FEV1 on days 1-7 following RV16UB challenge.

Hypothesis: The percent CFB in TWA evening FEV1 on days 1-7* after RV16UB infection will be less than zero on average. The expected mean TWA percent CFB (reduction) is at least -10%.

* Henceforth the TWA of a quantity over days *x* to *y* will be denoted *TWAx-y*.

Secondary outcome

3.2 Secondary Objective(s) & Hypothesis(es)

Study Part 2

(1) Objective: To estimate the CFB in FEV1 (maximum drop), and TWA3-10 in Asthma Control Diary (ACD) score.

Hypotheses: The mean CFBs in maximum drop FEV1, and increase in TWA3-10 ACD are different from zero.

(2) Objective: To estimate the within-subject Spearman correlations between maximum cold symptom score, TWA0-14 nasal virus titer (PCR), and each of TWA1-7 and max drop FEV1, maximum diary-based ACD and TWA3-10 of diary-based ACD.

Hypotheses: The within-subject Spearman correlations between maximum CSS,

TWA0-14 nasal virus titer, and each of TWA1-7 FEV1, maximum drop FEV1, and

TWA3-10 ACD will all be different from zero in the expected directions.

(3) Objective: To describe the course of virus shedding (PCR-quantitated)

following

challenge.

(4) Objective: To describe the virus-induced changes in high-dimensionality

clinical and biological phenotypes (*handprints*) of mild-moderate asthmatics

using the UBIOPRED multiscale systems medicine approach (*handprint analysis*).

This description includes all outcomes listed under primary, secondary and

exploratory objectives.

Study description

Background summary

Asthma is associated with chronic airway inflammation and misdirected immunity * resulting in bronchial smooth muscle hyperreactivity, mucus hypersecretion, and airway thickening.
This pathologic triad leads to acute and chronic airway obstruction. Asthma affects 6%-11% of the US population * annually resulting in ~3500 deaths and >400,000 hospitalizations [1, 2, 3]. Similar epidemiology is observed in Europe [39, 40], while worldwide, approximately 300 million people are affected [4]. Inhaled corticosteroids (ICS), long acting beta agonists (LABA), and cysteinyl leukotriene modulators have advanced
asthma care; nevertheless, a great number of people still have severe and/or poorly controlled asthma. Accordingly, these troublesome asthma subsets are the subjects of intense investigation * investigation that has been hampered by disease complexity, interpatient variability, and a poor mechanistic understanding of disease causality. These hurdles necessitate the study of large numbers of subjects and large numbers of biologic variables ineach patient. Accordingly, large consortia have arisen whose purpose it is to join the capabilities of multiple institutions to achieve the patient numbers and breadth of study seemingly required to understand severe and poorly controlled asthma [5,6,7]. The Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) consortium is the broadest such effort. It

attempts to characterize large numbers of asthmatics at high dimensionality and over time, in order to develop combined clinical and biological biomarkers of disease subtype, generate testable hypotheses about disease mechanism and treatment, and develop useful research tools for follow-on investigation.
U-BIOPRED operates under the aegis of the Innovative Medicines Initiative (IMI) * a pan- European public and private sector collaboration aimed at accelerating the discovery and development of better medicines for patients. IMI emphasizes the following steps in pursuing improved prediction of safety and efficacy of novel medicines: predictive pharmacology and toxicology, discovery of predictive biomarkers, patient studies, validation of biomarkers, and benefit/risk assessment. U-BIOPRED is the IMI consortium aimed at severe asthma [5]. Central to its approach is the development of *handprints* * high dimensionality descriptions of asthma that encompass demographic, clinical, imaging-based,
metabolic, transcriptomic, and genetic/genomic metrics. These complex descriptions will be used to develop multivariate biomarkers that correlate with asthma subtypes and their respective responses to pharmacologic intervention. The findings of U-BIOPRED will be
communicated with the world asthma community through conference presentations, publications, and special announcements
This study (PN218) is a component of the U-BIOPRED effort -- resultant data and specimens being shared with the members of the consortium to be analyzed in the larger context. Its purpose is to develop a standard virus challenge-based model of asthma exacerbation, and to
understand how patient handprints change in that context.

Study objective

The overarching goal is to qualify a virus challenge model for use in basic research and clinical development. This model will provide a consistent approach to generating and testing hypotheses relating to virally induced asthma exacerbations, and may provide better
positive prediction of efficacy in early development of new molecular entities (NME).
Furthermore, its adoption by many investigators will allow easier comparison of results from different laboratories since the same virus preparation and dosing approach will have been used.
PN218 is designed to achieve this goal in two steps. The first (Part 1) is to demonstrate tolerability of the RV16UB preparation at different dose levels with induction of expected cold symptoms at * 1 (one) dose level, and on an exploratory basis, to assess the reduction in
FEV1 induced by different virus challenge doses in the asthmatic panels.
The lowest tested dose that is both well-tolerated and induces satisfactory degrees of cold symptoms will be taken forward for the second step -- Part 2 for platform development, biomarker assessment, and handprint discovery.

Study design

This is a two-part nonrandomized, multicentre trial of a nasal rhinovirus challenge in healthy participants (hereafter also called *subjects*) and subjects with mild-moderate asthma to be conducted in conformance with Good Clinical Practices.
Part 1 is a dose-finding study of 1) up to 4 panels of up to 6 healthy volunteers and 2) up to 4 panels of up to 6 mild to moderate asthmatics not taking long-acting beta agonists (LABA), and 3) up to 4 panels of up to 6 mild to moderate asthmatics taking LABA -- each undergoing nasal challenge with U-BIOPRED human rhinovirus 16 (RV16UB) [also referred to in other study documents as "HRV-16" which all refer to the rhinovirus described in Section 4.1.1 and used in this study] at increasing doses in staggered fashion, as illustrated in Figure 1. The decision to start a panel of asthmatics at the next higher virus dose will be made after asthmatic participants in the previous panel have been safely challenged. The lowest dose asthmatic panel will begin the study at least one week after the first two panels of healthy volunteers have safely been challenged. Timing for dose advancement between panels with healthy volunteers and panels with asthmatics will be based on the appropriate amount of time needed to review safety data.
Part 2 is a longitudinal biomarker study of up to 25 mild to moderate asthmatics undergoing RV16UB challenge using the most appropriate dose identified in Part 1, based on tolerability and viral effects. This biomarker component is somewhat similar in structure to that used for each dose level in Part 1, with some changes in timing, procedures and number of visits. This protocol is written with some flexibility to accommodate the inherently dynamic nature of Experimental Medicine clinical trials. Please refer to Section 7.1.5 * Visit Requirements for modifications permitted within the protocol parameters. Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 * Trial Procedures.
1. Adaptive viral dose selection will be used in this study. Specifically, the dose of virus to be used in Part 2 will be determined from results of Part 1 as described in Section 5.2.1.2.
2. If a dose in the non-LABA taking panel in Part I is determined to be safe, the same dose does not necessarily need to be repeated in a panel of patients taking LABA. This is because participants taking LABA should be, in general, more protected against exacerbation-related AE's.

Intervention

There are no pharmacologic treatments being studied. This study involves a nasal rhinovirus challenge in both Parts 1 & 2 of the study.
In Parts 1 and 2, the rhinovirus challenge will occur on Day 0 (up to approximately 21 days post screening visit). Part 1 will determine the dose of

rhinovirus to be used in Part 2.
Part 1:
Starting Dose: Recent work has focused on low dose inoculations * on the order of 10 TCID50. In particular, work by S. Johnston at Imperial College, London [18] and by R.Lutter and K. van der Sluijs at University of Amsterdam [unpublished] strongly suggests that low dose inoculations are satisfactory for this approach. (Notably, the latter are investigators in this study.) To date, the only prominent difference between high -dose and low-dose approaches is a ~1-2 day delay in symptom peak * i.e. ~d6 vs. ~d4 for higher doses (see Figure 5 on page 21 of the protocol). Because the low-dose approach conserves virus stock, exposes participants to lesser amounts of virus preparation, and perhaps better reflects *natural* infection; 10 TCID50 will be the starting dose in Part 1.
The remaining doses span the range (up to 10,000 TCID50) of published experience with rhinovirus 16 and merit testing to verify similarity of potency between the RV16UB GMP preparation with other related stocks previously used. Hence, doses of 10, 100, 1000, and
10000 TCID50 are planned for PN218.
Part 2:
The dose selected for Part 2 will be the lowest dose for which: there are sufficient data from a
completed panel of asthmatic subjects, there are no concerns arising from key safety
variables, and the effect criteria of Primary Hypothesis #3 for Part 1 (Section 3.1) have been
met.

Study burden and risks

No tangible benefits accrue from participation in this clinical study. Participants will, however, know that they are helping to develop a standardized tool to enable a better understanding of asthma exacerbation. This understanding, coupled with the novel biomarkers and mechanistic hypotheses that may follow, may help advance asthma treatment * especially for patients with problematic asthma.

Risks to participants fall into two categories: (1) those associated with the challenge agent, and (2) those associated with the study procedures. Risks associated with the challenge agent can be subdivided into those associated with (a) the formulation and (b) the virus
infection itself. These are covered below.
(1a) As with any biologic preparation, the virus stock could induce immediate reactions resulting from contamination with toll-like receptor (TLR) agonists or other unintended bioactive materials. Furthermore, the preparations may be contaminated with infectious organisms other than the intended rhinovirus. To guard against this, manufacturing is cGMP compliant using well characterized cell stocks and growth media. Final virus

preparation is tested according to modern biologics manufacturing methods to rule out lipopolysaccharide contamination and the presence of microorganisms that could produce TLR agonists or frank infection. Because of these precautions and the fact that the seed stocks for the RV16UB preparation have been used in >100 subjects without any immediate reactions or unexpected infections, the probability of such events is considered to be very small.
(1b) The intended purpose/function of the RV16UB challenge agent is that of a functioning rhinovirus. Hence, a successful challenge means that participants will experience symptoms associated with the common cold. The common cold is a frequent event in human existence and does not confer particular risks except for those at the extremes of age, the immunosuppressed, and those with idiosyncratic susceptibilities or
severe underlying conditions. In asthma patients, the common cold may induce exacerbations characterized by chest symptoms and airflow reduction. Indeed, mild versions of this are a desired endpoint. To lessen risk of severe exacerbations necessitating oral steroids or acute medical attention, subjects will be of moderate age and will be screened for lack of non-asthma comorbidities, and for having only mildmoderate asthma with no history of asthma-related ICU admission or intubation during adult life. Furthermore, all asthmatic subjects will be maintained on their baseline inhaled corticosteroid regimens. Again, successful performance of dozens of published viral challenges in asthmatics -- without SAE and with less than a handful of required treatments with systemic steroids -- suggests that the approach is safe.
(2) Most study procedures such as phlebotomy, spirometry and nasal sampling entail minimal risk and are not covered here.
Induced sputum carries nominal risk of asthma exacerbation; however, its performance in many hundreds of published cases without such problems shows the risk to be low. The sponsor has performed >200 sputum inductions in allergen-challenged asthmatics over the past three years with no AEs beyond mild cough, wheeze, and chest discomfort; those AEs were occasional and either self-limited or controlled with an extra dose of salbutamol. The principal investigators have had similar experiences over many years of academic research. Of particular relevance to this study, peer-reviewed work has shown sputum induction to be safe -- even during exacerbations of asthma and COPD [41-43].
Risk will be mitigated in this study by pretreatment with inhaled beta agonists as well as by close monitoring of patient symptoms and airflow before, during, and after the procedure.

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. be willing to give written informed consent for the study - including future biomedical research on collected samples;
2. be able to read, comprehend, and write at a sufficient level to complete study materials;
3. be willing to complete the study and all measurements;
4. be male or female, aged 18 to 55 years of age (inclusive) at the pre-trial (screening) visit
5. have a Body Mass Index (BMI) * 35 kg/m2 and > 17 kg/m2. BMI <= weight (kg)/height (m)2.
6. for the purpose of safe participation, be judged to be in good health (except for allowable asthma) based on medical history, physical examination, vital signs, and laboratory safety tests (Section 7.1.3.1) performed at the pre-trial (screening) visit and/or prior to the rhinoviral challenge.
7. if a female subject, be one of the below:
- of childbearing potential and must demonstrate a serum *-hCG level consistent with the nongravid state at the pre-trial (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pre-trial visit throughout the trial and until 10 days after the last study visit.

- of non-childbearing potential: a female who is postmenopausal without menses for at least 1 year and an FSH level in the postmenopausal range at the pre-trial (screening) visit and/or a female who is status-post hysterectomy, status-post bilateral oophorectomy, or status-post bilateral tubal ligation without reversal based on the subject*s recall of their medical history. Information must be captured appropriately within the site's source documents.
8. be a nonsmoker or has not smoked in the past 12 months with a smoking history of * 10 pack-years;
9. be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).
10. have anti-hRV16 titers * 1:4 at the screening visit;
11. have negative nasal lavage rhinovirus PCR results prior to virus challenge;
Part 1:
12. be one of the following:
a. For healthy panels: healthy subject (may have out-of-season seasonal allergies)
b. For asthmatic panels: mild-moderate asthmatic with the below** criteria
Part 2:
13. have a diagnosis of mild-moderate asthma with the below** criteria.
** Inclusion Criteria for Mild-Moderate Asthmatics
(must be documented within the past five (5) years)
-- Diagnosis of asthma based on one or more of:
. Methacholine PC20 < 8 mg/mL
. Improvement in FEV1 after inhalation of 400mcg salbutamol of *12% of predicted value, and/or 200mL.
. diurnal variation in peak expiratory flow (PEF) >8% of mean of twice-daily PEF
. decrease in prebronchodilator FEV1 *12% of predicted FEV1 and/or 200mL after tapering off of inhaled corticosteroids (ICS), oral glucocorticoids, long-acting bronchodilator, or regular short-acting bronchodilator.;Note: in cases where either FEV1 or %FEV1 (but not both) changed by the amount specified above, admission of the candidate requires assent of the Sponsor.;AND
. a history of spontaneous or exertional wheezing
-- Controlled disease based on:
. pre-bronchodilator FEV1 * 80% predicted (may be established at screening)
AND having all the below for >4 weeks prior to screening
. daytime symptoms twice weekly or less
. no activity limitation
. no nocturnal symptoms
. use of reliever treatments twice weekly or less
. unchanged asthma medication dose
. use of ICS at a stable dose-equivalent of *500mcg/day fluticasone propionate
14. have had a mild exacerbation (e.g. change in symptoms leading to temporarily increased short acting beta agonist use or increased ICS dose) associated with viral syndrome within the past five (5) years. This will be assessed by patient interview.

Exclusion criteria

1. is mentally or legally institutionalized / incapacitated, has significant emotional problems at the time of pre-trial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 3 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator;
2. has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases;
-- Asthma as defined in the inclusion criteria for some participants in Part 1 and all participants in Part 2 is allowed.
-- Subjects with a history of uncomplicated (spontaneously evacuated, without infection) kidney stones, cholecystectomy or childhood asthma (the latter only for the healthy volunteer panels) may be enrolled in the trial at the discretion of the investigator.
3. has a history of cancer (malignancy) with the exception of uncomplicated basal cell carcinoma of the skin or cervical intraepithelial neoplasia - resolved for at least 5 years and not having required chemotherapy or immunomodulation;
4. has a history of severe or difficult to manage allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription
drugs or food, that in the opinion of the investigator would pose an undue risk to the subject;
5. has (or is expected to have) symptomatic seasonal or perennial rhinitis or sinusitis during the duration of the study (Can defer assessment until end of allergy season for seasonal allergies.);
6. has a history of ICU admission or intubation for asthma-related ventilatory failure in adolescence (after approximately age 11) or adulthood;
7. is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV;
8. has clinically significant abnormalities in screening laboratory tests or ECG;
9. has significant nasal septal deviation, nasal polyps, or other nasal anatomical abnormality;
Note: History of nasal corrective surgery is allowed if it occurred > 5 years prior to the pre-trial (screening) visit and healed normally.
10. shares the same household or has intimate contact with an infant, a pregnant or lactating woman, or an immunosuppressed individual;
11. has a history or current evidence of any upper or lower respiratory tract infection or symptoms of such within 6 weeks of baseline assessment (Can defer assessment until appropriate time has passed.);
12. had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pre-trial (screening) visit;
13. has participated in another investigational trial within 10 weeks prior to the pre-trial (screening) visit. The 10 week window will be derived from the date of the last trial medication and / or blood collection in a previous trial and/or AE related to trial drug to the pre-trial/screening visit of the current trial;

14. is pregnant or is a nursing mother;
15. is unable to refrain from or anticipates the use of prescription and/or non-prescription medications** or herbal remedies (such as St. John*s Wort [Hypericum perforatum]) beginning 2 weeks (or 5 half-lives) prior to administration of the initial dose of viral challenge, throughout the trial, until the post-study phone call;
Specifically excluded medications include montelukast and other leukotriene modifiers, oral or nasal corticosteroids, other immunomodulatory medications, longacting beta-agonists (in Part I for ICS-only cohorts) and inhaled anticholinergic agents.
**Exceptions: There are certain medications that are permitted, see Section 5.5;
16. consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Subjects that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator;
17. consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day;
18. is currently a regular user (including *recreational use**) of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years;
19. is considered by the investigator to be inappropriate for participation for any reason.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-11-2013
Enrollment:	49
Type:	Actual

Ethics review

Approved WMO Date:	16-10-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
CCMO	NL45122.018.13
Other	zie aanvullende opmerkingen