hVIVO

Respiratory Disease

Chronic/Acute Cough

THE CHALLENGE

Cough is the most commonly reported respiratory symptom, with acute cough being the most prominent symptom of the common cold. Acute cough is a cough lasting < 3 weeks and is often due to acute viral upper respiratory tract infections "URTI" with the symptom arising in over 80% of cases within the first 48 hours of infection. Acute cough challenge models have often used tussive agents such as capsaicin or citric acid. These challenges have been found to vary greatly in protocol design, agent used, delivery device, test end-point employed as well as inducing tachyphylaxis.

There is increased interest in compounds aimed at treating acute and chronic cough. There remains an unmet clinical need as current treatments demonstrate limited and/or unproven efficacy along with undesirable side effect profiles. Animal models of acute cough translate poorly to human studies. Most acute, post viral cough research to date has been in cell lines and has been reported specifically for human rhinovirus, "HRV". Naturally occurring acute cough has proven difficult to evaluate in humans due to uncontrolled variability relating to incubation time, virus sero-type, environment, as well as known placebo effects.

hVIVO has established the first human challenge model evaluating objective cough frequency and severity using one of the most common causes of cough, a viral infection, in a controlled clinical unit

ANTITUSSIVES

CONCEPTUAL OVERVIEW / CHALLENGE

Animal models of acute cough translate poorly to human studies

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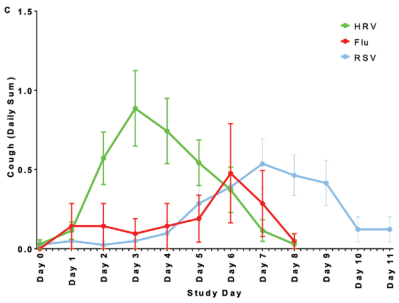
URTI is the most common cause of acute cough and so with a human challenge model incorporating a precision medicine approach, matching the drug MoA, population, study design and appropriate endpoints there is an opportunity for a unique positioning of an efficacious drug against chronic and acute cough

UTILISING HVIVO'S HRV CHALLENGE MODEL

- Evaluates awake cough frequency with and/or without drug during an acute viral infection using diary card or objective cough monitors
- Evaluates awake cough severity with and/or without drug during an acute viral infection using diary cards and/or related PRO's
- Evaluates drug efficacy on cough reduction during an acute viral infection
- Evaluates drug efficacy on reflex sensitivity (i.e. ATP challenge) during an acute viral infection
- Explores the relationship between genetic variation and response to the drug and mechanism of disease to validate endpoint for future use in later phase field trials
- Evaluates appropriate drug doses and associated AE's i.e. dysgeusia
- Give more precise and dynamic measurement of viral induced cough pathophysiology and drug MoA/efficacy
- Demonstrates direct effect on most common (i.e. URTI) cause of acute cough

Cough profile during an HRV-16, RSV and flu experimental infection



HVIVO HUMAN CHALLENGE MODELS FOR RESPIRATORY

VIRAL

HRV-16

Asthma HRV challenge in adults aged 18-60 years old

COPD HRV challenge in adults aged 40+ years old

NON-VIRAL:

- Bronchial Allergen
- LPS
- Histamine/Methacholine
- Adenosine Mono-Phosphate
- Adenosine Tri-Phosphate
- Mannitol

HVIVO'S HUMAN CHALLENGE MODEL AGENTS

hVIVO can offer a suite of viruses for use within human challenge models. These viruses have been used in numerous clinical trials with over 2500 patients/volunteers having been safely inoculated to date. We maintain a virus dossier as part of our commitment to safety and regulatory transparency.

hVIVO also has an extensive database of patient/volunteer virology and disease profile data giving us the ability to offer a unique insight into the human viral challenge model and has been, and will continue to be, a core part of our successful trial designs and client relationships.

- **HRV-16**
- **HRV-39**
- **RSV Memphis-37**
- **FLU H3N2**

HVIVO SERVICES FOR RESPIRATORY

Respiratory Diagnostics / Monitoring

Lung function (FEV_1, FVC, FEV_1/FVC, FEF_{25-75}, IC, SVC)

Reversibility

Forced Oscillation Technique

Cough Monitoring

Inflammation Sampling / Monitoring

Induced sputum

Fractional Exhaled Nitric Oxide (FeNO)

Nasosorption

Nasal Scrape

ABOUT HVIVO

Established in 1989 as a spin out from Queen Mary University, London, hVIVO is a trusted partner and industry leading clinical development services business pioneering human disease models based upon viral challenge. Using human challenge studies to establish early proof of concept, hVIVO's clinical trial platform can accelerate drug and vaccine development in respiratory and infectious diseases specifically leveraging hVIVO's established human disease challenge models in influenza 'flu', respiratory syncytial virus 'RSV' and human rhinovirus 'HRV' and more recently the expansion and development of these models in other respiratory indications for asthma, chronic obstructive pulmonary disease "COPD", cough and related new therapies and in special populations.

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* human rhinovirus (HRV) and respiratory syncytial virus