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Research Article

Phase 0 Experimental Medicine Study of Direct Intratarget Pulmonary Microdosing of nlrp3/1 Inflammasome Inhibitor ads032: the Micro Study. A Protocol Paper

T Quinn [1,3]*, A Bruce [2], S Dickson [1,2], E Gaughan [1,2], F Li[1], K Russell [1], R Wheeler [1], Joanne Mair [1], Katie Hamilton [1], A Akram [1,2], K Finlayson [1], N Hirani [1,2], K Dhaliwal [1,2]

[1]Baillie Gifford Pandemic Science Hub, Institute for Regeneration and Repair, Edinburgh BioQuarter, The University of Edinburgh, Edinburgh, UK.

[2]Department of Respiratory Medicine, New Royal Infirmary of Edinburgh, Edinburgh BioQuarter, Edinburgh, UK.

[3]Department of Respiratory Medicine, Western General Hospital, Edinburgh, UK.

***Corresponding Author:** Tom Quinn, Baillie Gifford Pandemic Science Hub, Institute for Regeneration and Repair, Edinburgh BioQuarter, The University of Edinburgh, Edinburgh, UK.

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Abstract:

Introduction

High attrition in drug development remains a significant challenge for research and development organisations worldwide. Most novel drug compounds fail at an early stage, often without knowledge of target engagement or molecular efficacy at diseased tissue level. Phase 0 trials provide an opportunity to provide mechanistic data in a small number of patients at the earliest stage of clinical development. The Micro study protocol is designed to deliver a microdose (100µg) of a novel inflammasome inhibitor ADS032 directly into the distal lung of patients with inflammatory and fibrotic interstitial lung disease and bronchiectasis with the aims of assessing feasibility, molecular efficacy and pharmacokinetics.

Methods and analysis

ADS032 (100µg) and vehicle will be delivered directly to the distal lung (intratarget microdosing) via a flexible catheter in patients undergoing bronchoscopy. Lung samples will be collected in the form of bronchoalveolar lavage, micro-alveolar lavage, and distal airway brushings Up to 12 patients will be recruited. The study is not randomised. The primary endpoint will be measurement of the inflammasome-pathway mediators IL-1β, TNF-α, LDH, ATP, IL-6 and IL-18 in BAL macrophages in the presence of ADS032. A secondary aim is to determine pharmacokinetic (PK) data for the microdosed drug in blood. Exploratory endpoints will include evaluation of a range of potential inflammasome mediators in other lung samples and PK data in urine and respiratory samples.

Ethics approval, data management and dissemination

The Micro study has received a favourable ethical opinion from South Central Oxford B Research Ethics Committee (REC) and approval from the National Health Service (NHS) Lothian Research and Development (R&D) department. The Medicines and Healthcare Products Regulatory Agency (MHRA) determined that the study is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) and therefore does not require MHRA regulatory oversight. Clinical data management (CDM) will be in accordance with standard National Health Service (NHS) Lothian Research and Development (R&D) regulatory requirements. The results will be submitted for publication in a peer-reviewed journal as soon as possible after recruitment and data analysis is complete.

Registration details

The Micro study is registered with the primary clinical trial register ISRCTN. The record number is ISRCTN35867933.

Highlights

1. This phase 0 Micro study adopts a novel intratarget microdosing lung protocol and is designed to provide feasibility evidence and first in human mechanistic data for a microdosed inflammasome inhibitor in human diseased lung.
2. Our data will inform the decision to progress the drug along the clinical development pathway.
3. Microdosing studies are not designed to address drug safety or clinical efficacy but can provide information regarding drug-target engagement.
4. The protocol is designed as a template for future lung intratarget microdosing studies.

Keywords: pharmacodynamics; pharmacokinetic; chronic lung disease

Introduction

High attrition in drug development remains a significant challenge for research and development (R&D) organisations worldwide. Reducing the attrition rate during clinical drug development is among the key requirements for improving R&D productivity and thereby increasing the number of drugs entering late phase trials [1,2]. Early characterisation of mechanism of action and pharmacodynamics (PD)-pharmacokinetic (PK) relationship in human disease before Phase 1 clinical trials would allow for more effective 'triaging' of preclinical candidates for entry into clinical development. Phase 0 studies, so named because they are positioned between pre-clinical and phase I stages, have no therapeutic intent and are not designed to study drug safety or tolerance, but are aimed at providing preliminary information regarding target engagement, mechanism of action, PD and PK [3,4]. These studies support the use of first-in-human testing of new investigational agents at sub-therapeutic doses (100µg or less). Their merit is based on reduced manufacturing and pre-clinical toxicologic and regulatory requirements while still allowing demonstration of drug-target effects and assessment of PK-PD relationships [5]. Phase 0 studies are particularly useful when there is incomplete understanding of mechanistic and PK/PD data from pre-clinical models [6,7]. if pre-clinical data suggests a high toxicity potential [8]. or if there are poor animal models for a human illness in which case early phase human trials may be the most appropriate model [9]. These challenges are frequently seen in chronic lung diseases and phase 0 trials have been utilised for respiratory drug development [10]. Interstitial lung diseases (ILD) are a group of inflammatory and fibrotic lung diseases amongst which a significant subgroup, such as idiopathic pulmonary fibrosis (IPF) and progressive fibrotic ILD (PF-ILD) are associated with a high burden of morbidity and mortality and effective treatment represents an unmet need. Non-cystic fibrosis (CF) bronchiectasis is a chronic suppurative lung disease characterised by cough, sputum production and frequent infections. The cycle of infection and inflammation leads to progressive lung damage. There is currently no disease modifying treatment for non-CF bronchiectasis. Despite the heterogenous aetiology and clinical features of these diseases, there may be some unifying molecular mechanisms. Inflammasome activation in alveolar macrophages (AM) has been shown in patients with IPF and other ILDs and sarcoidosis [11,12]. A subset of patients with bronchiectasis have evidence of inflammasome activation with high IL-1β sputum levels, mucus dehydration and ciliary dysfunction and more severe disease [13]. The inflammasome is therefore a potential target in ILD and non-CF bronchiectasis. The Clinical Investigational Agent (CIA), ADS032 (formerly known as BT032), is a novel nod-like receptor protein (NLRP) 1 and 3 inhibitor that has a promising pre-clinical toxicity and efficacy profile but has not been tested in humans. The Micro Study is a phase 0, experimental medicine study which will gather feasibility and mechanistic data of direct intrapulmonary dosing of ADS032 in patients with interstitial lung disease and bronchiectasis. This study seeks to test the hypotheses that microdosed ADS032 can attenuate inflammasome activity in chronic lung disease.

Methods and analysis

Study design

This is a small, exploratory Phase 0 experimental medicine study and as such formal sample size calculations have not been performed. ADS032 or vehicle will be microdosed into the distal lung during a bronchoscopic procedure, ensuring administration in different distal lung locations. Samples will be taken from all patients prior to, during and after the procedure to determine the activity and distribution of ADS032.

Patient and Public Involvement

There was no patient or public involvement in the design, conduct or reporting of the Micro trial.

Target population

Patients with suspected or confirmed ILD or bronchiectasis requiring bronchoscopy for clinical indications including diagnosis and exclusion or qualification of infection.

Inclusion and exclusion criteria

Inclusion criteria:

- Provision of informed consent.
- Aged at least 18 years.
- Diagnosis of suspected or confirmed ILD or bronchiectasis and scheduled to have a bronchoscopy.
- Is not participating in a Clinical Trial of an Investigational Medicinal Product (CTIMP).

Exclusion criteria:

- Pregnant or breastfeeding.
- Known hypersensitivity to ADS032.
- In the Investigator's opinion, patient is unwilling or unable to undergo a bronchoscopy, laboratory tests or other study procedures.
- ILD and bronchiectasis patients receiving steroids or other immunomodulators (defined as any drugs that may suppress the immune system - azathioprine, mycophenolate, ongoing chemotherapy, macrolide antibiotics).

Endpoints

The primary endpoint will be changes of BAL concentrations of inflammasome-associated mediators IL-1β, TNF-α, LDH, ATP, IL-6 and

IL-18A between ADS032 and vehicle areas of lung. The secondary endpoint will be to determine pharmacokinetic (PK) data for the microdosed drug in blood. Exploratory endpoints will include the evaluation of a range of potential inflammasome mediators in lung samples and urine/respiratory sample PK.

Dosing regime

Bronchoscopy will be performed as per local clinical guidelines which include conscious sedation and topical, locally delivered anaesthetic. Up to 100µg of ADS032 (approximately 1.5 mL) will be delivered into the distal lung using a medically approved catheter. This can be administered as a single dose or smaller divided doses. The target area/s will be identified on chest X-ray (CXR)/ computerised tomography (CT) scan prior to the bronchoscopy and then aspirated using a medically approved catheter. Patients will serve as their own controls as an equivalent volume of 0.9% sodium chloride saline (vehicle) will be delivered to an area/s of diseased lung that has not been dosed with ADS032 and aspirated using a medically approved catheter. Medically approved devices will be used to perform the bronchoscopic sampling techniques bronchoalveolar lavage (BAL), micro-alveolar lavage (MAL) and distal airways brushings. Both BAL and distal airway brushings are commonly described procedures [14,15]. BAL will deploy 1x40ml instilled aliquots and MAL will deploy 1-2mL instilled aliquots pre- and post- drug/vehicle delivery.

Sample processing and analyses

Briefly BAL samples with be centrifuged to separate the cellular fraction. BAL distal epithelial cells will be analysed by morphology and multiparameter flow cytometry utilising lineage markers to determine phenotype. Flow cytometry and analysis of early cytokine responses with ELISA and multi-plex platform will be performed along with bulk and single cell (sc)RNA-seq to investigate cellular activity in response to ADS032. BAL cells will be cultured and treated with inflammasome activators including LPS and assayed for transcriptional and cellular and secreted mediator expression. Cell lysates, BAL and MAL fluid, plasma and urine will be assayed for ADS032 concentrations with a validated LC-MS.

Statistics and data analysis

Sample size calculation

This is an early-stage feasibility and experimental medicine study and as such the sample size has been based upon the number of participants we can expect within the time frame and a cohort size intended to provide preliminary information for future studies. The number of participants (n=12) is in line with successfully completed Phase 0 trials in NHS Lothian with other microdosed compounds.

Proposed analysis

Descriptive statistics will be used to evaluate three aspects of ADS032:

· Change in inflammasome-associated biomarkers between pre- and post ADS032 or vehicle in respiratory samples.

· Quantification of ADS032 in blood, urine and respiratory samples using liquid chromatography-mass spectrometry (LC-MS).

· Change in exploratory biomarkers between pre- and post ADS032 or vehicle in respiratory samples.

All data will be listed, tabulated and/or presented graphically as suitable to the dataset and objective. Where appropriate summary statistics may be complemented with statistical tests and confidence intervals to aid in interpretation of magnitudes of effect and the likelihood of results occurring by chance.

For target pathway engagement, PK and exploratory biomarkers the estimand of interest is that which gives the most unbiased estimate of the impact of ADS032. As such all data will be included unless specific data points can a priori be identified as having potential to bias results in which case they will be excluded. An intent-to-treat approach will be taken to safety reporting, such that all subjects enrolled will be included.

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