Methods selective TRPV1 antagonist in animal and human models. would offer substantial symptom control. SB705498 is a potent esise that topical antagonism with a selective TRPV1 antagonist responsiveness resulting in symptoms in NAR patients. We hypoth- thought to play a key role in the development of nasal hyper- stress. In the nose, the TRPV1-expressing sensory c-fibres are

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SB705498 was very well tolerated. approximately 5 hrs post dose, in keeping with previous studies. Diary Card symptoms, RQLQ or Nasal Airflow. Tmax occurred at

Diary Card symptoms, RQLQ or Nasal Airflow. Tmax occurred at

Results monitoring.

recorded, as was acoustic rhinomanometry, RQLQ, PK and Safety

norrhoea, congestion, PND), sneezing and ocular symptoms were

and Day 14+24hr to establish the drug response. Post dose TSS (rhi- tent diagnosis with a single challenge on Day 1+1hr, Day14+1hr

Skin prick testing, at screening were performed to establish a consis-

chamber sessions of 1hr duration, as well as medical history and neg

ting home dosing on days when the temp was less than 14c. T wo

two of all fibre types were

were detected using both antibodies. Co-staining revealed that only

PGP9.5 defined pulmonary neuroendocrine cells and better eluci-

detected using appropriate Alexa-fluor conjugated secondary anti-

PGB9.5, Leica Biosystems, UK) were applied at a dilution of

Primary antibody binding was

using 10% normal serum and 1% skimmed milk powder, diluted in

paraformaldehyde. Non-specific antibody binding was blocked

out the extrapulmonary airways, was immediately fixed in 4%

were detected using both antibodies. Co-staining revealed that only

PK analysis supported an.o.d. regimen with 2 fold accumulation over the dosing period.

Conclusions In a robust clinical model of allergic rhinitis, there was no intrinsic activity demonstrated by SB705498 and no addi- tive effect on a background of intranasal steroids. FP was highly effective in this study. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, sug- gesting redundancy in symptom pathways.

Abstract P153 Figure 1

TRPV1 IS NOT A TARGET FOR THE TREATMENT OF NON-ALLERGIC RHINITIS: A CLINICAL STUDY

doi:10.1136/thoraxjnl-2012-202678.215

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Background TRPV1 is a ligand gated ion channel activated by a range of physiological factors such as Temperature, pH, and osmotic stress. In the nose, the TRPV1-expressing sensory c-fibres are thought to play a key role in the development of nasal hyper- responsiveness resulting in symptoms in NAR patients. We hypoth- esise that topical antagonism with a selective TRPV1 antagonist would offer substantial symptom control. SB705498 is a potent selective TRPV1 antagonist in animal and human models.

Methods 40 M&F NAR patients were enrolled into a randomised, double-blind, placebo controlled, 2 period crossover study of either 12mg SB705498 i.n. or placebo for 14 days with a 4 week washout. The study was conducted in a validated Environmental Challenge Chamber (Cetero) where patients were exposed to Cold Dry Air (CDA) at 14c, 15% RH, air speed 5 feet/sec. Exposure was over the winter months in Canada. Diary card symptoms were analysed during home dosing on days when the temp was less than 14c. Two chamber sessions of 1hr duration, as well as medical history and neg skin prick testing, at screening were performed to establish a consist- tent diagnosis with a single challenge on Day 1+1hr, Day4+1hr and Day 14+24hr to establish the drug response. Post dose TSS (rhinorhoea, congestion, PND), sneezing and ocular symptoms were

recorded, as was acoustic rhinomanometry, RQLQ, PK and Safety

monitoring.

Results The primary outcome of weighted mean TSS over the challenge period or the maximum TSS was not impacted by administra- tion of SB705498 relative to placebo (see figure). There was no impact on sneezing, ocular symptoms, acoustic rhinomanometry, or RQLQ. Compared with placebo, repeated doses of SB705498 did not alleviate TSS triggered by cold in a multistimuli wild type setting.

Conclusions In a robust clinical model of allergic rhinitis, intranasal SB705498 12mg o.d. for 14 days did not alleviate the symptoms of NAR triggered by the most common provocation agent: Cold Dry Air. We conclude that despite engagement of the TRPV1 receptor there was no translation to clinical efficacy, sug- gesting redundancy in symptom pathways.

Abstract P154 Figure 1

P155 VISUALISATION OF AIRWAY NERVES IN CHRONIC COUGH: TOWARDS THE IDENTIFICATION OF THE HUMAN 'COUGH RECEPTOR'

doi:10.1136/thoraxjnl-2012-202678.216

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Introduction The spinal and vagal innervation of the respiratory tract is well defined, particularly in animals. These discoveries include the identification of pathways involved in provoking cough and descriptions of the guinea pig ‘cough receptor’. However, many of the immunohistochemical features of the airway afferents described in animals have yet to be defined in humans, yet plasticity of these airway afferents may be important in the pathophysiology of chronic cough.

Objectives To define and characterise the innervation present in bronchoscopic biopsies from patients with chronic cough. We aimed to carry out the first ever whole mount immunohistochemical studies of airway nerves in cough patients, a technique that should improve visualisation of these neuronal structures and their sites of termination.

Methods Biopsy tissue was gifted from patients undergoing clini- cal investigation for chronic cough. Tissue, sampled from through- out the extrapulmonary airways, was immediately fixed in 4% paraformaldehyde. Non-specific antibody binding was blocked using 10% normal serum and 1% skimmed milk powder, diluted in PBS, before application of primary antibodies. Polyclonal rabbit anti-FCP9.5 (Ultraline, UK) and monoclonal mouse anti-neurofil- ament (NF200, Leica Biosystems, UK) were applied at a dilution of 1:1000 and 1:200 respectively. Primary antibody binding was detected using appropriate Alexa-fluor conjugated secondary anti- bodies and whole mount preparations were visualised using epifluo- rescence and confocal microscopy. Images of biopsy staining were subject to morphometric analysis.

Results Many epithelial, subepithelial and intramuscular fibres were detected using both antibodies. Co-staining revealed that only PGP9.5 defined pulmonary neuroendocrine cells and better eluci- dated varicose epithelial fibres. A proportion of all fibre types were

Thorax 2012;67(Suppl 2):A1–A204