# Safety and efficacy of PrEP-001, a novel immunomodulator, for prevention of viral respiratory infection in subjects with asthma

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## Background

Upper respiratory viral infections (URVIs) represent a significant unmet medical need for people with asthma as they are triggers of up to 85% and 50% of exacerbations in pediatric and adult asthmatics respectively[1]. Of the URVIs that cause exacerbations, the vast majority are rhinoviruses and coronaviruses, viruses for which we have no approved vaccines or antivirals.

Most URVIs start in the nasal epithelium and the local cellular innate immune response is the body's initial response and defense against these infections. PrEP-001 Nasal Powder, is a proprietary formulation of polyriboinosinic and polyribocytidylic acid (poly I and poly C) which acts as a benign viral surrogate to elicit an innate immune response locally in the nasal epithelium via TLR-3, Rig-I and MDA5. Prior viral challenge studies using rhinovirus 16 (HRV16) and influenza A (H3N2) in healthy volunteers demonstrated that prophylaxis with PrEP-001 prevents common cold and influenza illness and reduces the severity and duration of associated symptoms[2]. Therefore this exploratory HRV16 challenge study (NCT03296917) was conducted to assess the safety and efficacy of PrEP-001 in subjects with mild to moderate asthma.

## Methods

Otherwise healthy asthmatic (GINA Steps 1 to 3) males or females aged 18 to 55 years with a forced expiratory volume ($FEV_1$) ≥60% of predicted normal value were eligible. Smokers and ex-smokers were excluded. Subjects with a history of life-threatening asthma, or recent exacerbation were also excluded. In the Viral Challenge Arm, subjects were excluded if they had neutralizing antibody titers to the challenge virus >1:8 at screening.

The double-blind, placebo controlled study comprised a safety arm (without viral challenge) and an HRV16 challenge arm. The study was not powered on Total Symptom Score (TSS), but 20 subjects per group was considered suitable based on previous HRV16 challenge studies in healthy subjects.

Safety Cohort: 20 asthma subjects were randomized. Two groups of 6 were given two successive daily doses of PrEP-001 (6.4 mg or 12.8 mg/day) and two groups of 4 were given matching placebos. Normal adverse event and safety monitoring, including spirometry and nasal epithelial fluid sampling, was conducted.

Viral Challenge Cohort: 39 asthma subjects were randomized 1:1 to receive either PrEP-001 (6.4 mg/day) or placebo for two days. 24 hours after the second dose of PrEP-001, subjects were inoculated with 10 $TCID_{50}$ of HRV-16 (2 X 25 ml per nostril) and monitored in individual quarantine for the next 8 days. Symptoms measured using a modified Jackson questionnaire (10 respiratory symptoms measured on a scale of 0-3) three times per day.

Nasal epithelial lining fluid samples were obtained using Synthetic Absorptive Matrices[3] prior to and following dosing and evaluated for antiviral and pro-inflammatory cytokines (TNF-α, IP-10, eotaxin, eotaxin-3, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, TARC, IL-5, IL-16, IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4, IL-6, IL-8, IFNα-2a, IFN-γ) using V-plex and Pro-inflammatory multiplex kits from MSD (Meso Scale Diagnostics, Rockville, MD).

## Design

Safety Cohort:
- 6.4mg (n=6), 12.8mg (n=6) PrEP-001 or placebo (n=8) dosed on 2 consecutive days
- No viral challenge
- Subjects not quarantined

Monitor subjects

Nasal sampling in both arms: Wicks 2 times / day

Time (days) -2 -1 0 1 8

Viral Cohort:
- 6.4mg PrEP-001 (n=19) or placebo (n=20) dosed on 2 consecutive days (Day -2 & -1)
- HRV-16 challenge on Day 0
- Subjects quarantined (Day -4 to Day 8)
- 10 Symptoms measured by modified Jackson questionnaire (score 0-3) TID

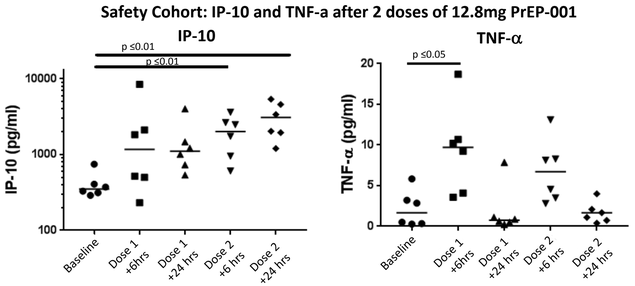
HRV16 Challenge

Monitor subjects

## Safety Cohort: Biomarkers

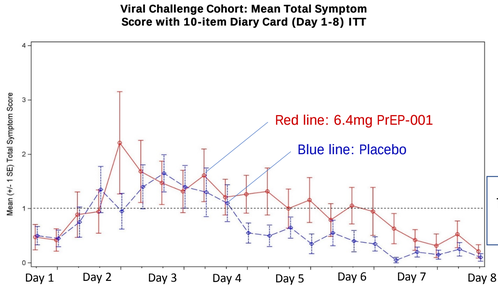
- Despite the small size of the Safety Study, several cytokines and chemokines, IP-10, TNF-α, IL-1b, IL-6, IL-8 and eotaxin, showed significantly higher levels in nasal epithelium fluid following administration of PrEP-001 (Mann-Whitney U test). No significant changes were observed on the other cytokines tested.
- In the Safety Cohort, median levels of TNF-α and IP-10 rose significantly (i.e. TNF-α: 2 to 10 pg/ml, p=0.01, IP-10: 750 to 4010 pg/ml, p=0.03) following the administration of PrEP-001 (either 6.4 mg or 12.8 mg).
- As IP-10 was the most robust biomarker identified in the Safety Cohort and indicative of innate immune response, it was selected for analysis in the Viral Challenge Cohort.

## Biomarkers in Nasal Epithelial Lining Fluid




## Results from Viral Challenge Cohort

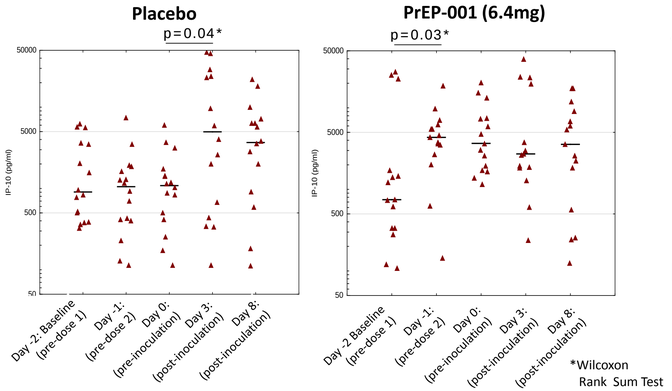
- 18 subjects (94.7%) in the PrEP-001 group and 18 subjects (90.0%) in the placebo group had laboratory-confirmed infection.
- There was no detectable effect of PrEP-001 on AUC TSS, the primary endpoint, or on secondary endpoints involving symptom severity or viral load.
- Despite causing infection, the virus generated an unexpectedly low level of symptoms: median (range) Total Symptom Score AUC (min.TSS) were 4796.6 (0-46141) and 4072.3 (482-21653) in the PrEP-001 and placebo groups respectively.




TSS level of 1 means one mild symptom

## IP-10 Induction in the Viral Challenge Cohort

- Evaluation of nasal epithelium fluid showed robust, consistent elevation of IP-10 in PrEP-001 treated individuals suggesting that it had elicited the expected effect on the local innate immune response.
- Levels of IP-10 in PrEP-001 treated individuals were comparable to those seen following viral inoculation in the placebo group.




## IP-10 Induction in the Viral Cohort (cont.)

- PrEP-001 induced changes in IP-10 levels in subjects with asthma were similar to those observed in healthy volunteers (Malcolm et al., ATS 2018 poster 13240 - Safety and Nasal Cytokine Response of PrEP-001, a Novel Immunomodulatory Nasal Spray for Prophylaxis of Respiratory Viral Infections).

## Combined Safety Results

- 6.4mg and 12.8mg PrEP-001 was generally safe and well tolerated. There were no SAEs.
- Most treatment emergent adverse events (TEAEs) were mild. No subjects were withdrawn from the study because of TEAEs.
- No treatment-related TEAE was considered probably or definitely related to PrEP-001.
- No significant changes were observed between PrEP-001 12.8mg 6.4mg and placebo groups for any lung function or other asthma specific parameter (i.e. PEF, FEV1, FeNO).

## Conclusions

- PrEP-001 Nasal Powder appears to be safe and well-tolerated in asthma subjects with no adverse clinical pulmonary effects.
- PrEP-001 administration generates significant induction of IP-10, TNF-a, IL-1b, IL-6, IL-8 and eotaxin.
- Nasal IP-10 induction following PrEP-001 was as expected and comparable to that observed as a result of the HRV16 viral infection in the placebo group.
- Despite creating apparent infection, viral inoculation in this study generated an unexpectedly low level of symptom levels in the placebo group making the efficacy results of PrEP-001 prophylaxis in asthma subjects inconclusive.
- Further testing with larger sample sizes will be necessary to determine the clinical benefit in asthma subjects.

## References:

[1] Gern JE, J Virol. 2010;84:7418-26.
[2] Malcolm et al, J Antiviral Research 2018; 153:70-77.
[3] Hansel et al. 2017, EBioMedicine 19, 128–138.