Safety and nasal cytokine response of PrEP-001, a novel immunomodulatory nasal spray for prophylaxis of respiratory viral infections

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Background

PrEP-001 Nasal Powder, a proprietary encapsulation of polyriboinosinic and polyribocytidylic acid (poly I and poly C), elicits a cellular innate immune response locally in the nasal lining. Two prior viral challenge studies explored 6.4mg PrEP-001 given to healthy volunteers on two consecutive days followed by a rhinovirus (HRV-16) or influenza A (H3N2) challenge 24 hours after the second dose[1]. They demonstrated that PrEP-001 prevented or reduced the severity and duration of common cold and influenza illness. A subsequent clinical trial involving HRV16 challenge 3 days or 6 days after PrEP-001 dosing demonstrated that the prophylactic efficacy wanes within 3 days of the last dose.

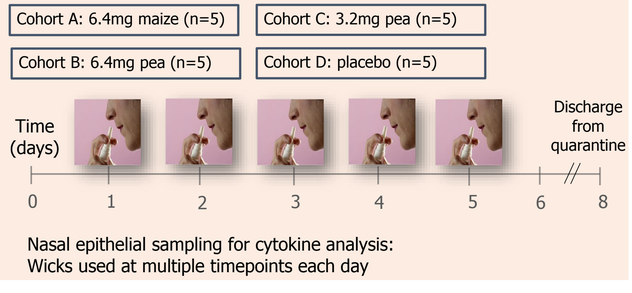
Cytokine activation is observed 6 hours after PrEP-001 dosing and robust and consistent responses are observed 24 hours after a first and second dose of both 6.4mg and 12.8mg of PrEP-001. However the duration of cytokine elevation and magnitude of response following multiple doses and lower dose levels was unknown.

This study assessed the safety and nasal cytokine response to 3.2mg and 6.4mg of PrEP-001. In addition the cytokine response to PrEP-001 Nasal Powder manufactured at low (Formulation A) and high (Formulation B) concentration using different starches to deliver 6.4mg of API using either 4 or 2 sprays per nostril was compared. Challenge studies conducted previously used Formulation A.

Methods

Using a randomized, placebo-controlled approach, 20 healthy male volunteers aged 18-65, were administered PrEP-001 (6.4mg, n=10 Formulation A or B; 3.2mg, n=5 Formulation B) or placebo to match Formulation B (n=5) once daily for 5 days. Formulation A contained PrEP-001 at low concentration in maize starch and Formulation B contained PrEP-001 at a higher concentration in pea starch. Nasal lining fluid was sampled using Synthetic Absorptive Matrices[2] prior to and following each dose and assessed for IP-10 and TNF-a levels using MSD (Meso Scale Diagnostics, Rockville, MD) microtiter plate assays.

Design



Results: Safety

- PrEP-001 was safe and well tolerated with a profile similar to placebo. There were no deaths, SAEs or discontinuations.
- All TEAEs were mild.
- The most frequently reported TEAEs were procedural haemorrhage (18 [90%] subjects), nasal mucosal disorder (17 [85%] subjects) and nasal crusting (15 [75%] subjects). The incidence of these events was similar across all treatment groups including placebo.
- There were no clinically significant changes in any laboratory parameters, vital signs or ECG recording observed for any subject during the study.
- Serum MCP-1 concentration was measured in the 6.4mg PrEP-001 Formulation B arm and saw no notable change from baseline indicating a lack of systemic effect.

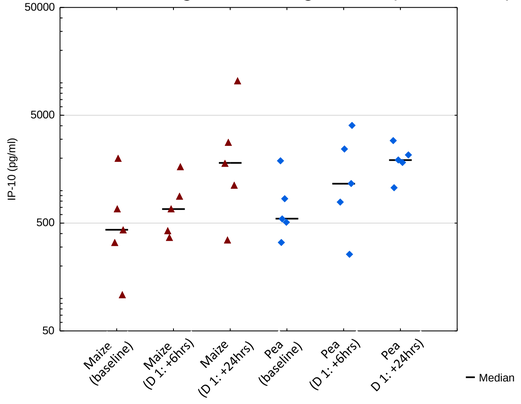
Results: Cytokines

Nasal cytokines (IP-10 and TNF-α) following administration of 6.4mg of Formulation A and B of PrEP-001

IP-10 and TNF-α were selected as markers of the nasal innate immune response.

- IP-10 in nasal epithelial fluid increased from median concentrations of 434 and 550 pg/ml at baseline to median concentrations of 1810 and 1920 pg/ml 24 hours after the first dose in the Formulation A and B groups respectively.
- As there was no difference between the results for 6.4mg doses from Formulation A and B, all results for this dose have been combined for subsequent analysis.
- Similar responses were observed in the 3.2mg PrEP-001 group.
- No meaningful changes were observed in the placebo group.

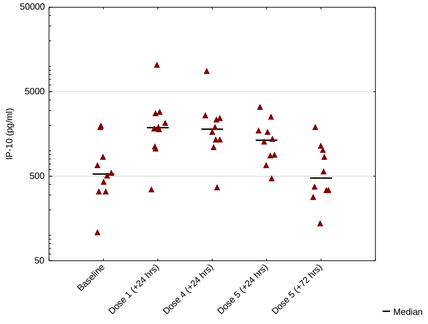
Nasal IP-10 following 1 dose of 6.4mg PrEP-001 (Maize and Pea)



IP-10 response following 5 days of 6.4mg PrEP-001

- In the 6.4mg arms (n=10), median IP-10 concentration increased from 531pg/ml at baseline to 1880pg/ml 24 hours after the first dose (p-value = 0.011 Mann-Whitney U test).
- 24 hours after the 4th and 5th doses of 6.4mg PrEP-001, median IP-10 was 1805pg/ml and 1335pg/ml respectively, suggesting neither tachyphylaxis nor a cumulative dose effect.
- IP-10 levels returned to baseline within 72 hours of the last dose.

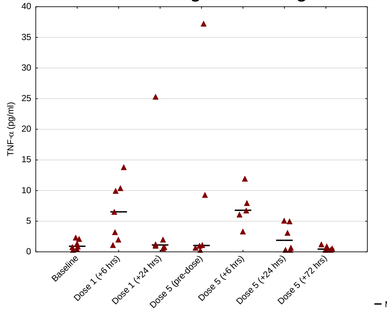
Time course of nasal IP-10 during & after PrEP-001 administration



TNF-α response following 5 days of 6.4mg PrEP-001

- One batch of TNF-α samples failed reducing the number of subjects with reportable data to n=7.
- In the combined 6.4mg arms, median TNF-α levels increased from 0.9 pg/ml at baseline to 6.5 pg/ml within 6 hours of the first dose.
- TNF-α levels returned to baseline within 24hrs of each dose.
- Median TNF-α levels were comparable 6 hours after the first and fifth dose, suggesting neither tachyphylaxis nor a cumulative dose effect.
- No meaningful changes were observed in the placebo group.

Time course of nasal TNF-α during & after 6.4mg PrEP-001 administration

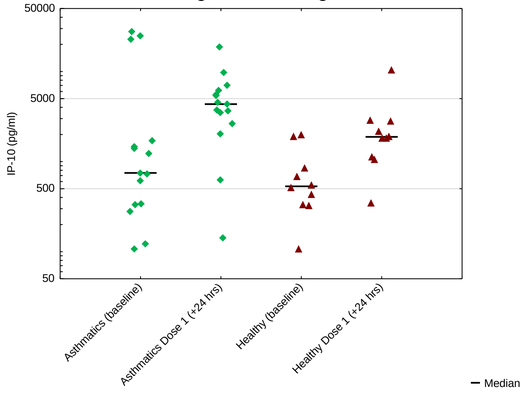


Cross Study Comparison

IP-10 induction is similar between healthy volunteers and GINA 1-3 asthmatics following administration of PrEP-001

- IP-10 induction from the 6.4 mg cohorts of this study in healthy volunteers was similar to IP-10 induction observed in GINA 1-3 asthmatic volunteers (see ATS poster 13146) following administration of PrEP-001 in a separate clinical trial.

Comparison of nasal IP-10 in asthmatic and healthy subjects following 1 dose of 6.4mg PrEP-001



Conclusions

- 5 consecutive daily doses of 3.2mg and 6.4mg PrEP-001 appeared safe and well tolerated.
- No systemic effect (as measured by serum MCP-1) was observed following nasal administration of 6.4mg PrEP-001.
- Daily dosing produced a rapid, stable elevation of IP-10 and consistent rise and fall of TNF-α indicated a lack of tachyphylaxis or cumulative dose effect with short-term dosing of PrEP-001.
- The return of cytokine levels to baseline within 72 hours of the last dose provides a mechanistic explanation for the lack of clinical efficacy seen in a prior HRV-16 challenge study examining weekly and bi-weekly dosing.
- These results provide rationale for exploring daily dosing in future studies.

References:

[1] Malcolm et al, J Antiviral Research 2018; DOI: 10.1016/j.antiviral.2018.03.005.
[2] Hansel et al. 2017, EBioMedicine 19, 128–138.