Safety and Tolerability of the Toll-Like Receptor (TLR)2/6 Agonist INNA-051 in Healthy Adults

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ENA RESPIRATORY

Introduction

Antiviral innate immunity in upper respiratory tract is the first line of defense against respiratory viruses. ENA Respiratory is developing a Toll-like receptor (TLR) 2/6 agonist delivered via intranasal spray, for use as an innate immune pan-antiviral that can be self-administered over short or long periods for the prevention of complications associated with respiratory viral infections. Pre-clinical studies demonstrate that INNA-051and analogues are effective against a variety of respiratory viruses including SARS-CoV-2, influenza, and rhinovirus. INNA-051 induces a tissue-localized innate immune response with cytokine expression and infiltration of innate immune cells into the nasal epithelium that play a key role in viral clearance. The primary objective of this study was evaluation of safety and tolerability in healthy adults.

Methods

The First Time In Human (FTIH) study INNA-051-HVT-01 was a randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics (PD) of single and multiple ascending intranasal (i.n.) INNA-051 doses in healthy adults (18-55 years old) and healthy older volunteers aged >65yrs. The study was conducted in three parts:

Part A, a Single Ascending Dose (SAD) evaluation;

Part B, a Multiple Ascending Dose (MAD) evaluation; and

Part C, a MAD evaluation in healthy older volunteers aged >65yrs [Aged MAD cohort].

Eight healthy volunteers participated in each SAD and MAD cohort and 12 in the "Aged MAD" cohort. Subjects were allocated to placebo and active treatment in a ratio of 1:3. In the MAD study, the interval between doses is 3 days, and the number of administrations used is 4. Safety and tolerability were assessed through collection of adverse events, visual analog scale (VAS) scores for nasopharyngeal symptoms, clinical laboratories, and measurement of peak nasal inhalation flow (PNIF) and peak expiratory flow (PEF).

Outcomes

Intranasal INNA-051 was well tolerated across all cohorts up to single doses of 600µg and multiple doses of 300µg. Mild, self-limited nasal adverse events were observed and are possible indicators of tissue-localized innate immune response by INNA-051. No significant systemic adverse events were noted and there was no remarkable impact on PNIF or PEF. Investigation of cytokine levels and gene expression of the intranasal epithelium are in progress to specifically determine TLR2/6 engagement by INNA-051. The results from this study support progression of INNA-051 into Phase 2 clinical evaluation.

Results

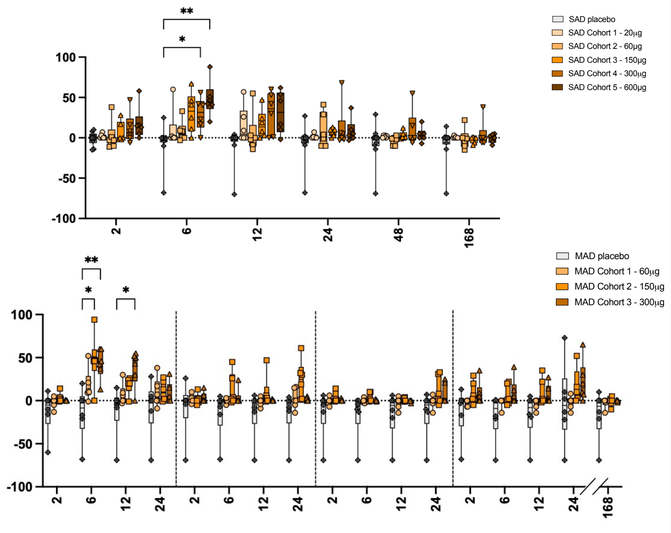
Table 1: SAD Incidence of 3 or More Treatment-Emergent Adverse Events

System Organ Class (SOC) Preferred Term (PT)	INNA-051 20 ug (N=6) n (%) E	INNA-051 60 ug (N=6) n (%) E	INNA-051 150 ug (N=6) n (%) E	INNA-051 300 ug (N=6) n (%) E	INNA-051 600 ug (N=6) n (%) E	Pooled Placebo (N=10) n (%) E
Nervous system disorders						
Headache	1 (16.7) 1	1 (16.7) 1	2 (33.3) 2	2 (33.3) 2	2 (33.3) 3	2 (20.0) 2
Respiratory, thoracic and mediastinal disorder						
Nasal congestion	0	3 (50.0) 3	4 (66.7) 4	2 (33.3) 2	6 (100.0) 6	2 (20.0) 2
Nasal inflammation	0	0	0	0	2 (33.3) 2	1 (10.0) 1
Nasal mucosal disorder	0	4 (66.7) 4	4 (66.7) 4	6 (100.0) 6	2 (33.3) 2	1 (10.0) 1
Nasal oedema	0	1 (16.7) 1	2 (33.3) 2	0	0	0
Rhinorrhoea	2 (33.3) 2	2 (33.3) 2	3 (50.0) 3	2 (33.3) 2	3 (50.0) 3	0
Sneezing	0	0	0	0	3 (50.0) 3	0

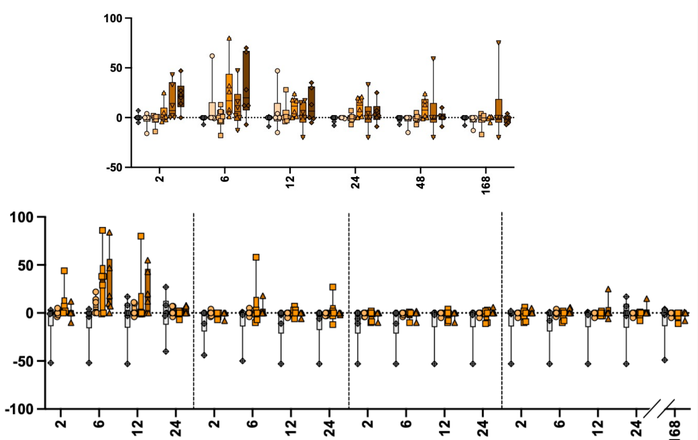
Table 2: MAD Incidence of 3 or More Treatment-Emergent Adverse Events

System Organ Class (SOC) Preferred Term (PT)	INNA-051 60 ug (N=6) n (%) E	INNA-051 150 ug (N=6) n (%) E	INNA-051 300 ug (N=6) n (%) E	Pooled Placebo (N=6) n (%) E	INNA-051 300 ug Elderly (N=8)	Placebo Elderly (N=4) n (%) E
Nervous system disorders						
Headache	2 (33.3) 4	1 (16.7) 2	2 (33.3) 2	1 (16.7) 1	3 (37.5) 4	2 (50.0) 2
Respiratory, thoracic and mediastinal disorders						
Nasal congestion	4 (66.7) 5	6 (100.0) 9	5 (83.3) 7	4 (66.7) 4	3 (37.5) 4	0
Nasal discomfort	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	0	1 (12.5) 1	0
Nasal inflammation	5 (83.3) 8	2 (33.3) 4	5 (83.3) 10	1 (16.7) 1	7 (87.5) 11	1 (25.0) 4
Nasal mucosal disorder	4 (66.7) 6	6 (100.0) 10	5 (83.3) 9	4 (66.7) 9	5 (62.5) 6	2 (50.0) 2
Oropharyngeal pain	1 (16.7) 1	2 (33.3) 2	2 (33.3) 2	0	1 (12.5) 1	1 (25.0) 1
Rhinorrhoea	2 (33.3) 3	3 (50.0) 4	1 (16.7) 1	1 (16.7) 1	5 (62.5) 7	1 (25.0) 1
Sinonasal obstruction	0	0	0	1 (16.7) 1	2 (25.0) 2	0
Throat irritation	1 (16.7) 1	1 (16.7) 1	0	1 (16.7) 2	0	0

Normalized VAS – Nasal Blockage



Normalized VAS – Rhinorrhoea



Nasal Blockage and Rhinorrhoea VAS Scores in SAD, MAD and Aged MAD Cohorts Normalized (baseline subtracted) nasal blockage and rhinorrhoea VAS scores in SAD cohorts 1-5 (A), MAD cohorts 1-3 (B) and Aged MAD cohort (C) were analyzed by two-way mixed model ANOVA with Dunnett's (or Šídák's – Aged cohort only) correction for multiple comparisons to placebo. *p<0.05, **p<0.005