Clinically Relevant Reductions in FeNO Reported After 10-day Treatment With KN-002 in Subjects With Mild Asthma

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Introduction

- The JAK-STAT pathway mediates activity of multiple pro-inflammatory cells, cytokines and chemokines implicated in the pathogenesis of non-eosinophilic and eosinophilic severe asthma.
- KN-002 is a potent and balanced pan-JAK inhibitor[1], formulated as a dry powder for delivery via inhalation.
- Delivery of KN-002 results in high lung bioavailability, low plasma exposure, inhibition of Th1/2/17 pro-inflammatory mediators, attenuation of STAT phosphorylation levels and suppression of house dust mite induced airway hyper-responsiveness[2,3].

Study Objectives

Primary

- Assess the **SAFETY AND TOLERABILITY** of multiple ascending doses of **INHALED** KN-002 in subjects with stable mild asthma

Secondary

- Changes in **FeNO** from Day 1 pre-dose to Day 10 and % subjects with Day 10 FeNO levels <25 ppb
- Characterisation of **PLASMA** pharmacokinetics (PK) via C_{max}, T_{max}, $T_{1/2}$, area under the curve and accumulation ratio for C_{max} and area under the curve

Study Methods

Study Design

- Part 2 of a 4-part Phase 1b, randomized, double-blinded, placebo-controlled study (NCT05006521)
- Subjects in clinic for 12 days; follow-up at Day 17
- **10-DAY TREATMENT PERIOD**

Doses/regimen (6 active:2 placebo)

- 0.6 mg QD, 2 mg QD, 4 mg BID and 8 mg BID

Subjects

- Aged 18-65 years with physician diagnosis of asthma
- **NAÏVE TO ICS THERAPY WITH FeNO ≥30 PPB**
- Body mass index ≥ 18 and ≤ 35 kg/m^2
- Pre-bronchodilator FEV_1 ≥ 70% predicted

Study Results

Table 1: Study Demographics

Baseline parameter (mean)	Overall (ITT) Population	
	Active (n=24)	Placebo (n=8)
Age (years)	35.5	47.5
Gender (% male/female)	83/17	88/13
BMI (kg/m^2)	26	27
FeNO (ppb)	74.5	48.2
Pre-dose FEV_1 (% pred)	85	80
Blood eosinophil count (10^6/L)	323	229

Safety

- No deaths, serious or severe adverse events (AE), dose changes or withdrawals
- **ALL AES MILD OR MODERATE AND UNRELATED TO TREATMENT.**
- No treatment related or clinically important hematologic or chemistry findings.

Pharmacokinetics

- Dose proportional PK profile (AUC and C_{max})
- **MAXIMUM UNBOUND KN-002 PLASMA CONCENTRATIONS BELOW PHARMACOLOGICALLY ACTIVE LEVELS[1]**
- Steady state PK achieved by Day 3
- Minimal accumulation in plasma after 10-day repeat dose period (C_{max} ratio 1.1 to 1.9, AUC_{TAU} ratio 1.2 to 1.8)
- Main metabolite at 1% of parent in plasma

Table 2: Mean KN-002 Plasma PK Parameters at Day 10

Parameter	0.6 mg QD (n=6)	2 mg QD (n=6)	4 mg BID (n=6)	8 mg BID (n=6)
C_{max} (ng/ml)	2.0	6.5	31.5	60.4
$AUC_{0\text{-}12}$ (ng.h/ml)	16.1	55.2	236.8	458.2
T_{max} (hours)	2	3	2	2
$T_{1/2}$ (hours)	9.2	8.4	14.1	20.6

Pharmacodynamics

- **CLINICALLY RELEVANT (>20%) LS MEAN PLACEBO-CORRECTED FeNO REDUCTIONS, FROM DAY 1 PRE-DOSE TO DAY 10 MEAN, ACHIEVED WITH 2 mg QD (-27.9% [95% CI,-56.6, +0.8]), 4 mg BID (-28.4% [95% CI, -55.3,-1.5]) AND 8 mg BID (-24.1% [95% CI, -50.1, +1.9]) REGIMENS**
- 0.6 mg QD established as minimally active dose (LS mean placebo corrected reduction -7.4% [95% CI, -33.5,+18.7])
- Clinically relevant placebo-corrected reductions achieved as quickly as Day 1
- FeNO reduction continues to at least Day 10 and is maintained post 2-day no treatment period
- FeNO values revert to near Day 1 pre-dose levels after a 7-day no treatment period
- **67% OF SUBJECTS RANDOMISED TO 4 mg BID ACHIEVE NORMAL FeNO VALUES (<25 PPB) AT DAY 10**
- Maximal PD effect achieved with 4 mg BID regimen; no additional benefit with 8 mg BID regimen

Figure 1: FeNO change from Day 1 pre-dose to Day 17

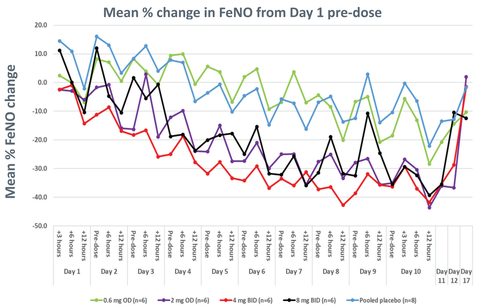

Table 3: Table 3: KN-002 responder analysis at Day 10

Dose/regimen	% subjects with FeNO <25 ppb on Day 10
Pooled placebo (n=8)	13
0.6 mg QD (n=6)	17
2.0 mg QD (n=6)	17
4.0 mg BID (n=6)	67
8.0 mg BID (n=6)	50

Conclusions

- **No safety concerns post 10-day administration of daily doses ≤16 mg**
- **Unbound plasma levels below pharmacologically active concentrations**
- **Clinically relevant FeNO reductions achieved with ONCE- AND TWICE DAILY REGIMENS**
- **Maximal FeNO response with 4 mg BID regimen delivered via a SINGLE capsule**
- **Outcomes support evaluation of 4 mg BID in subjects with moderate/severe asthma and COPD**

References: [1] Wiegman C. ERJ 2015; 46: PA2130; [2] Wiegman C. AJRCCM 2015; 191:A6435; [3] Wiegman C. J Aerosol Med Pulm Drug Del 2015: 28(3):A23-A23.

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