Pharmacokinetics and Pharmacodynamics of the Phosphodiesterase 4 (PDE4) inhibitor HPP737 Following Single-dose Administration in Healthy Subjects

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- **Single dose administration of HPP737 was well tolerated with no dose limiting safety/tolerability findings**
- **Pharmacokinetics supports once daily administration**
- **Functional pharmacologic activity consistent with PDE4 inhibition at doses ≥ 12mg**

Introduction

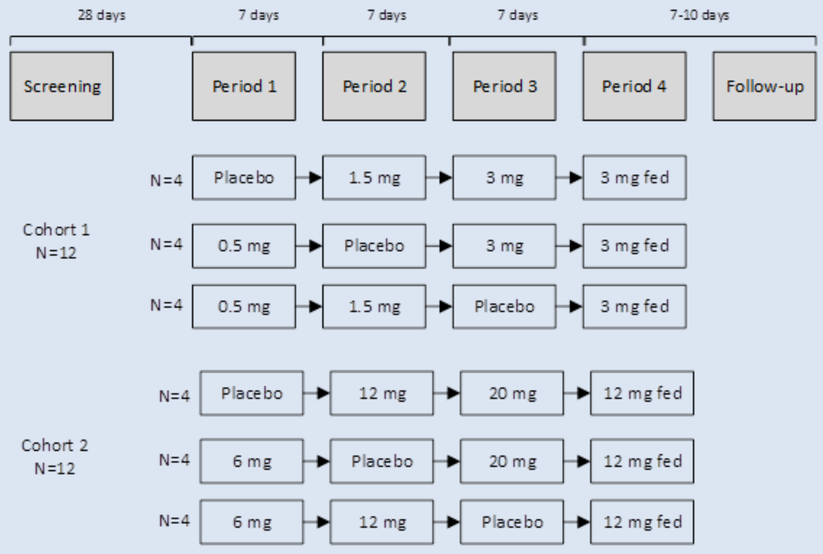
HPP737 is an oral, potent and selective PDE4 inhibitor in clinical development for the treatment of psoriasis. PDE4 inhibition represents a precedented mechanism for the treatment of moderate to severe psoriasis and atopic dermatitis with commercially available therapies for each indication. HPP737 was developed with properties of increased selectivity for PDE4B2 vs. PDE4D, limited CNS penetrance / limited PDE4D mediated activity in the locus coeruleus, and increased potency (10-100x) compared to approved PDE4 inhibitors. These attributes suggest the potential for HPP737 to exceed the efficacy of PDE4 inhibitors for moderate to severe psoriasis, with lower doses and avoidance of the side effects typically associated with oral PDE4 inhibitors. This First in Human study assesses the safety and tolerability of HPP737 in healthy subjects.

Objectives

- To evaluate the safety and tolerability of HPP737 following single ascending dose administration to healthy subjects
- To evaluate the single dose pharmacokinetics (PK) of HPP737 including assessment of the effect of food (i.e. FDA high-fat meal)
- Exploratory objective to assess the effect of HPP737 on ex-vivo, whole blood, LPS stimulated TNF-α

Methods

- Phase 1, single-blind, within cohort single ascending dose, 3-period crossover design with placebo substitution (under fasted conditions)
- A fourth open-label period evaluated the PK of HPP737 administered after a breakfast (FDA high-fat meal)



- Clinical laboratories, ECG, vital signs performed serially over 60h post dosing
- Blood sampling for HPP737 PK serially over 60h post dosing
  - PK analyzed by non-compartmental analysis
- Blood sampling serially over 48h post dosing for ex vivo TNF-α response
- Urine collection of 48-hour for HPP737 urinary excretion

Results

Safety / Tolerability

- Single dose HPP737 safe and well tolerated in healthy volunteers
- No dose-limiting adverse events
- No clinically significant changes observed in clinical laboratory, ECG, vital sign parameters
- Maximum investigated dose (20mg) limited to exposure in 28-day tox studies available at time of study

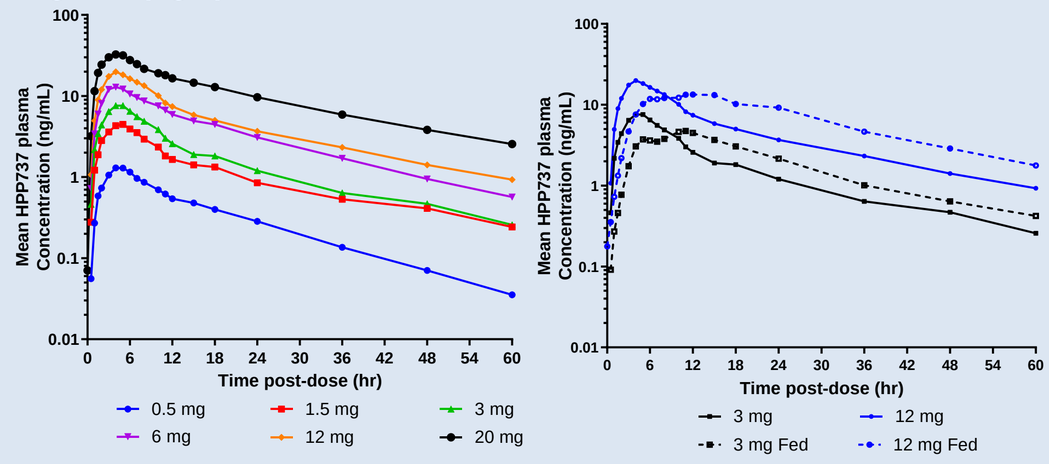
Treatment Ermergent Adverse Events (TEAEs) – All Causality

Adverse Event Preferred Term	Placebo (n=24)	HPP737 Dose Group							
		0.5 mg (n=8)	1.5 mg (n=8)	3 mg (n=8)	6 mg (n=8)	12 mg (n=7)	20 mg (n=8)	3 mg Fed (n=12)	12 mg Fed (n=12)
Number of Subjects with at least 1 TEAE	2 (8.3%)	0	1 (12.5%)	2 (25%)	1 (12.5%)	0	2 (25%)	3 (25%)	0
Total number of adverse events	3	0	1	2	1	0	3	5	0
Headache	1 (4.2%)	0	1 (12.5%)	0	1 (12.5%)	0	1 (12.5%)	0	0
Dizziness	0	0	0	0	0	0	0	1 (8.3%)	0
Dyspepsia	0	0	0	1 (12.5%)	0	0	0	0	0
Excoriation	0	0	0	0	0	0	1 (12.5%)	0	0
Feeling hot	0	0	0	0	0	0	0	1 (8.3%)	0
Limb injury	0	0	0	1 (12.5%)	0	0	0	0	0
Nausea	0	0	0	0	0	0	1 (12.5%)	0	0
Somnolence	0	0	0	0	0	0	0	1 (8.3%)	0
Vision blurred	0	0	0	0	0	0	0	1 (8.3%)	0
Vomiting	0	0	0	0	0	0	0	1 (8.3%)*	0
Crying	1 (4.2%)	0	0	0	0	0	0	0	0
Influenza like illness	1 (4.2%)	0	0	0	0	0	0	0	0

* Occurred 3 minutes post dosing

Pharmacokinetics

HPP737 mean plasma concentration vs time. Fasted (left); 3mg and 12mg FED (right)



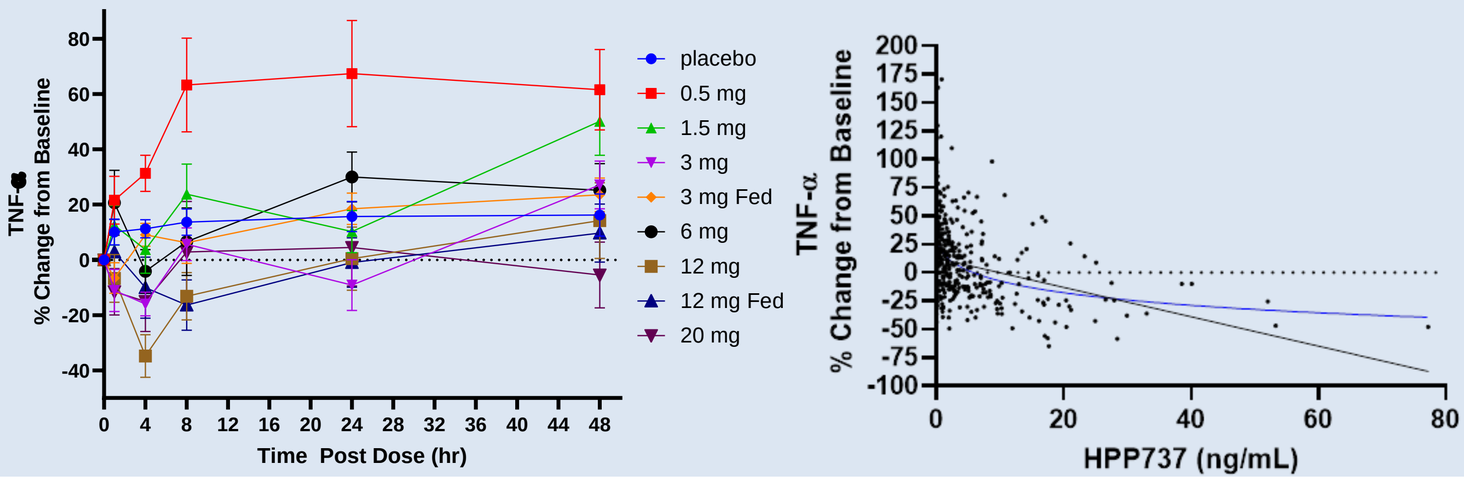
PK Parameter	0.5 mg (n=8)	1.5 mg (n=8)	3 mg (n=8)	6 mg (n=8)	12 mg (n=7)	20 mg (n=8)
C_{max} (ng/mL)	1.35 ± 0.501	4.67 ± 1.80	7.88 ± 1.82	13.3 ± 5.37	21.2 ± 8.59	35.5 ± 22.6
T_{max} (h)	4.0 (4.0, 8.0)	5.0 (4.0, 5.0)	4.5 (3.0, 5.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (2.0, 6.0)
AUC_{0-24} (ng*h/mL)	14.8 ± 8.47	49.5 ± 24.4	78.4 ± 22.2	155 ± 83.2	212 ± 93.1	424 ± 289
AUC_{0-inf} (ng*h/mL)	25.8 ± 12.7	72.6 ± 41.6	110 ± 36.6	220 ± 133	327 ± 148	705 ± 403
t1/2 (h)	17.3 ± 6.83	19.4 ± 5.26	21.1 ± 13.3	14.7 ± 4.16	17.1 ± 5.44	19.0 ± 3.77

Results reported as mean ± SD except Tmax reported as median (range)

- Dose proportional increase in exposure
- Linear PK
- <1% excreted as unchanged drug in urine
- Food effect:
  - 3mg: no food effect on AUC, ~37% decrease Cmax
  - 12mg: mild food effect (~29% increase) on AUC, no effect on C_{max}

Pharmacodynamics

Ex-vivo TNF-α. Mean (SE) % change from baseline over 48h (left). % change from baseline vs. HPP737 concentration (right)



- At 12mg and 20mg doses, numerical decrease in TNF-α noted at ~HPP737 Tmax
- Trend for greater TNF-α reduction with increasing HPP737 concentration (linear regression [black line] and sigmoid inhibitory Emax model [blue curve])
- Potential opportunity for increased PD effect with further exploration of higher HPP737 concentrations.

The results of the current single-dose study supported advancement of HPP737 into multiple ascending dose studies in healthy subjects to assess the safety, tolerability and pharmacokinetics of HPP737.

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