Phase 1, Single Ascending Oral Dose Study of the Safety, Tolerability, and Pharmacokinetics of a Novel HIV-1 Maturation Inhibitor in HIV Negative Healthy Subjects

Andrew Beelen, James Otto, Matthew Fidler, Elizabeth Sanguinetti, Patricia Smiley, Alfred Balch, Matthew Medlock[a], Mary Jackson, Edward Swabb

Myriad Pharmaceuticals Inc., Salt Lake City, UT, USA & [a] PPD, Inc., Austin, TX, USA

Abstract # K-119
Myriad Pharmaceuticals, Inc.
320 Wakara Way
Salt Lake City, UT 84108
USA
Tel:(801) 883-5073
Fax: (801) 883-3213
abeelen@myriad.com

Abstract

BACKGROUND:
MPC-9055 is a potent, orally bioavailable, small molecule inhibitor of human immunodeficiency virus-1 maturation. MPC-9055 targets a unique cleavage event in the HIV life cycle by inhibiting processing of the viral capsid protein p25 to p24. Inhibition of this final step in Gag processing leads to the noninfectious virion and thereby prevents subsequent rounds of HIV infection.

METHODS:
This was a first-in-human, single oral dose, double blind, placebo controlled, sequential escalating design study to evaluate the safety, tolerability and pharmacokinetic parameters of MPC-9055 under fasted and fed conditions. The fasted dose levels were 1, 2, 4, 8, 16, 32 and 48 mg/kg. The fed dose levels were 8 mg/kg (high fat) and 16 mg/kg (low fat). *An additional cohort of eight subjects was enrolled to assess the relative bioavailability of an oral tablet formulation. Safety measurements included physical exams, ECGs, vital signs, laboratory parameters, and adverse event monitoring. Pharmacokinetic parameters were summarized and dose-proportionality was assessed using a log-log model.

RESULTS:
Safety: A total of 63* subjects received active drug and 20 received placebo. No serious adverse events or clinically significant laboratory trends or ECG changes were observed. Overall, 30%* of subjects who received active treatment experienced at least one treatment emergent adverse event (AE) compared to 15% who received placebo. The most common AEs in the active treatment groups were nausea, diarrhea, and lightheadedness*. All AEs were of mild intensity with the exception of 1 AE of moderate intensity diarrhea.
Pharmacokinetic: In the fasted cohorts, mean half-life ranged from 23-42 hours, T_{max} ranged from 2-4 hours and C_{max} and AUC values increased with increasing dose in a sub-linear fashion. AUC increased approximately 2-fold following either a low-fat or high-fat meal relative to the fasted state. C_{max} was also increased in both fed states and T_{max} and apparent half-life were not significantly changed.

CONCLUSIONS:
MPC-9055 had a favorable safety and pharmacokinetic profile following single dose administration to healthy volunteers. A multiple dose study in HIV infected individuals is planned.

**New data added to poster after abstract submission*

Objectives

- Primary: Characterize the safety and tolerability of MPC-9055
- Secondary:
  - Characterize the pharmacokinetic parameters of MPC-9055 in the fasted state
  - Assess the effect of a low fat and high fat meal on the PK parameters of MPC-9055
  - Assess the relative bioavailability of an oral tablet

Study Design

- Single oral, escalating dose, double blind, placebo controlled
- Fasted dose levels were 1, 2 , 4, 8, 16, 32 and 48 mg/kg as oral solution
- Fed dose levels were 8 mg/kg high fat; 16 mg/kg low fat as oral solution
- Tablet dose level was 600 mg (3 x 200 mg tablets)

Subject Selection

Key Inclusion Criteria:
- Healthy adult male and/or non-childbearing potential female subjects
- 18-55 years of age.
- Body mass index (BMI) between 18-30, inclusive.
- Medically healthy subjects; ALT, BUN, urine protein, and serum creatinine within the reference range.
- Subjects must be nonsmokers.

Key Exclusion Criteria:
- History or presence of a significant medical condition
- History of alcoholism or drug abuse within the past 12 months.
- Use of any prescription medication (with the exception of hormone replacement therapy) within 1 month of Day-2.
- Routine use of any over the counter medication, including herbal supplements, within 2 weeks prior to Day -2.
- Donation of blood within 30 days prior to Day-2.
- Participation in another clinical study within 30 days of Day-2.
- Hemoglobin < 12.0 g/dL (females), hemoglobin < 14.0 g/dL (males).

Criteria for Evaluation

- Safety: The primary endpoints of this study included clinical signs and symptoms from the physical examination, adverse events, laboratory safety (hematology, serum chemistry, and urinalysis), and vital signs.
- Pharmacokinetic: The secondary PK endpoints included:
  - $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, T_{max}, $T_{½}$
  - Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48 and 72 hours after administration of MPC-9055

Statistical and Pharmacokinetic Methods

- Safety: Vital sign measurements, laboratory values, and the incidence of adverse events were summarized using descriptive statistics.
- Pharmacokinetic: PK parameters for plasma concentration-time data for MPC-9055 were derived by non-compartmental analysis using WinNonLin® Professional V5.1.1. AUC and C_{max} were analyzed using a linear model on log-transformed data and relative bioavailability was calculated as the ratio of exposures for the fed to fasted states. Summary statistics were calculated for key PK parameters for all treatment groups.

Demographics and Baseline Characteristics

	MPC-9055 (N= 63)	Placebo (N=20)
Age (years)		
Median (Min, Max)	29 (18,54)	29 (20,55)
Gender		
Male	52 (82.5%)	14 (70.0%)
Female	11 (17.5%)	6 (30.0%)
Weight (kg)		
Mean±SD	77.2 ±12.84	70.6 ±7.93

Treatment Emergent Adverse Events

Preferred Term	MPC-9055 (N=63)	Placebo (N=20)
Nausea	8 (12.7%)	
Diarrhea	5 (7.9)	
Lightheadedness	3 (4.8)	
Abdominal Cramping	2 (3.2)	
Headache	2 (3.2)	
Loose Stool	2 (3.2)	
Viral Syndrome	2 (3.2)	1 (5.0%)
Allergic Rhinitis	1 (1.6)	
Belching	1 (1.6)	
Cold Symptoms	1 (1.6)	
Decreased Appetite	1 (1.6)	
Drowsiness	1 (1.6)	
Fatigue	1 (1.6)	
Flushing	1 (1.6)	
Increased Frequency of Defecation	1 (1.6)	
Muscular Leg Cramping	1 (1.6)	
Near Syncope	1 (1.6)	
Throat Discomfort	1 (1.6)	
Tiredness	1 (1.6)	
Muscular Pain Right Leg		1 (5.0)
Musculoskeletal Low Back Pain		1 (5.0)

Treatment Emergent Lab Parameters

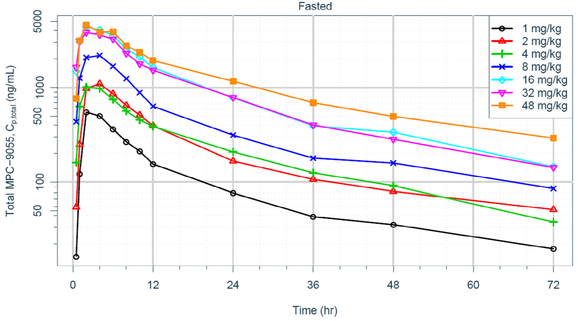
Lab Test	DAIDS Grade	MPC-9055 (N=63)	Placebo (N=20)
ALT (IU/L)	1	1 (1.6%)	1 (5.0%)
AST (IU/L)	1	1 (1.6)	
	2	1 (1.6)	
Bilirubin Total (mg/dL)	1	4 (6.3)	1 (5.0)
Hypercalcemia (mg/dL)	1	2 (3.2)	
Hypercholestermia(mg/dL)	1	20 (31.7)	7 (35.0)
	2	5 (7.9)	3 (15.0)
Hyperglycemia (mg/dL)	1	1 (1.6)	1 (5.0)
Hypoglycemia (mg/dL)	2	1 (1.6)	
Hypernatremia (mmol/L)	1		1 (5.0)
Hyponatremia (mmol/L)	1	9 (14.3)	2 (10.0)
Triglycerides (mg/dL)	2		1 (5.0)
Prothrombin Time	2	1 (1.6)	1 (1.6)

Summary of Pharmacokinetic Parameters by Cohort

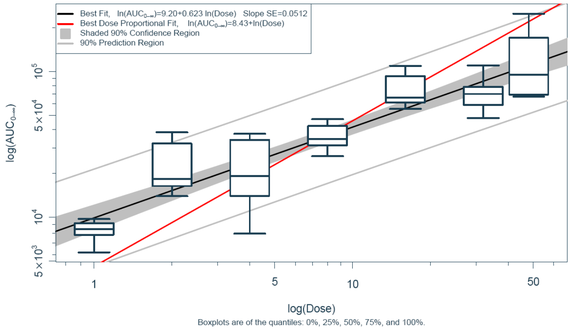
Parameter	Dose (mg/kg; N=6) 1	2	4	8	8[a]	16	16[b]	32	48
$AUC_{(0-\infty)}$ (ng*hr/mL) Geometric Mean 90% CI	8014 (7779-8256)	21,736 (18,635-25,353)	19,296 (13,969-26,655)	35,477 (34,039-36,975)	66,853 (65,039-68,719)	73,902 (69,055-79,089)	125,959 (114,896-138,087)	70,020 (65,337-75,038)	110,736 (84,868 - 144,489)
C_{max} (ng/mL) Geometric Mean 90% CI	547 (447-669)	1323 (1195-1465)	1328 (772-2286)	2605 (2477-2740)	3282 (3180-3387)	4849 (4635-5074)	8386 (8028-8759)	4068 (4014-4123)	5157 (4562-5830)
T_{max} (hr) Mean±SD 90% CI	3.0±1.7 (1.6-4.4)	3.3±1.0 (2.5-4.2)	2.7±1.0 (1.8-3.5)	3.3±1.0 (2.5-4.2)	6.0±3.3 (3.2-8.8)	3.7±1.5 (2.4-4.9)	4.0±0.0 (4.0-4.0)	3.0±1.7 (1.6-4.4)	4.7±3.9 (1.4-7.9)
$T_{½}$ (hr) Mean±SD	31.3±7.5	43.0±12.9	26.6±7.8	28.4±9.7	29.1±12.0	23.9±5.9	25.7±7.5	23.7±4.2	28.2±6.4

[a] Fed, high fat; [b] Fed, low fat

Median Plasma MPC-9055 Concentration-Time Profiles



Dose Proportionality Evaluation
log($AUC_{0-\infty}$) vs. log(Dose), box−plots



Boxplots are of the quantiles: 0%, 25%, 50%, 75%, and 100%.

Food Effect

(N = 6)	High Fat[a]	Low Fat[b]
$AUC_{(0-\infty)}$ Ratio (90% CI)	1.9 (1.5 - 2.3)	1.7 (1.2 - 2.4)
C_{max} Ratio (90% CI)	1.3 (1.0 - 1.6)	1.7 (1.4 - 2.2)

Geometric LS mean ratio (Fed vs. Fasted)
[a] 8 mg/kg; [b] 16 mg/kg

Conclusions

- MPC-9055 had a favorable safety profile following single, oral dose administration in healthy volunteers
- Most adverse events were mild with the most common being nausea, diarrhea, and lightheadedness
- Food increased MPC-9055 exposure nearly 2-fold
- Plasma concentrations increased in a less than dose proportional manner

Acknowledgements: Wendy Painter M.D. and Tiffany Reyes

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