MPC-7869, a Selective Aβ42-Lowering Agent, Displays No Significant CYP2C9 Drug-Drug Interaction: A Phase 1 Study

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MPC-7869 Clinical Rationale

- Novel anti-amyloid treatment strategy for AD
- Selective Aβ42-Lowering Agent (SALA) *in vitro* & *in vivo*
  - Allosteric modulation of γ-secretase
- Reduces insoluble amyloid in mouse brain
- Improves spatial reference learning and memory performance in mice
- Effective concentrations in animal models are achievable in humans at doses that have been well tolerated
- Phase 3 trials of MPC-7869 in subjects with mild AD are ongoing

Background and Objectives

- Due to the high comorbidity documented in AD patient populations, this study was initiated to explore the potential for drug/drug interactions
- Previous studies revealed that CYP2C9 was the Cytochrome P450 enzyme most inhibited *in vitro* with an estimated inhibition constant within the range of anticipated therapeutic concentrations
- This study was conducted to:
  - 1) evaluate the effect of MPC-7869 (R-flurbiprofen) on drugs metabolized by CYP2C9 as measured by tolbutamide* clearance and pharmacokinetics
  - 2) develop a rationale for the safe use of MPC-7869 when given as a concomitant medication

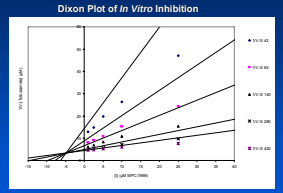
*Yuan R, et al. Evaluation of cytochrome P450 probe substrates commonly used by the pharmaceutical industry to study in vitro drug interactions. Drug Metab Dispos. 2004 Dec; 32(12): 1317-9.

MPC-7869 *In Vitro* P450 Inhibition Spectrum

Enzyme	IC_{50} Value
CYP1A2	>1000 μM
CYP2A6	>1000 μM
CYP2C8	200 μM
CYP2C9	4.8 μM*
CYP2C19	500 μM
CYP2D6	>1000 μM
CYP2E1	>1000 μM
CYP3A4	>1000 μM
UDPGT	300 μM

*Ki Value

In Vitro Inhibition of Cytochrome P450 Enzyme CYP2C9



Dixon plot illustrating the inhibitory effect of MPC-7869 and Ki value of 4.8 μM using human liver microsomes with model overlay (marker substrate: tolbutamide at 42, 84, 140, 280 and 420 μM).

Study Design

- Third party-blind, placebo-controlled, 2-period, crossover
- Subjects were treated to steady-state with MPC-7869 (800 mg BID) or placebo during each period
- Steady-state verified Study Days 4 & 5
- Single dose of tolbutamide (500 mg) given on morning of Day 6
- PK samples collected for 96 hours
- 14-day washout between last dose of period 1 and first dose of period 2

Study Endpoints

- The primary endpoints are the PK parameters of tolbutamide following each tolbutamide dose
- The secondary endpoints are as follows:
  - Clinical signs and symptoms from physical exam
  - Adverse events
  - Laboratory safety (hematology, serum chemistry, urinalysis)
  - Vital signs (blood pressure, heart rate, temperature, respiratory rate)

Inclusion Criteria

Subject candidates fulfilled all of the following inclusion criteria prior to participation in the study:

- Were healthy adult male and/or female subjects, 18 – 55 years of age
- Weighed at least 132 pounds for males and 105 pounds for females and were within 15% of their ideal weights (Table of "Desirable Weights of Adults," Metropolitan Life Insurance Company, 1983)
- Were medically healthy with no clinically significant screening results
- Provided voluntarily consent to participate in the study
- Females with childbearing potential, were either abstinent for 4 days prior to screening and throughout the study or used one of the following acceptable birth control methods:
  - IUD in place for at least 2 months prior to Day 1 of Period 1
  - Barrier method (condom or diaphragm) with spermicide
  - Stable hormonal contraceptive for at least 3 months prior to Day 1 of Period 1 through completion of study
  - Surgical sterilization (vasectomy) of partner at least 6 months prior to Day 1 of Period 1
- Females without childbearing potential were
  - Naturally postmenopausal for a minimum of 2 consecutive years prior to Day 1 of Period 1
  - Surgically sterile (bilateral tubal ligation with surgery at least 6 months prior to Day 1 of Period 1, hysterectomy, or bilateral oophorectomy with surgery at least 2 months prior to Day 1 of Period 1)

Exclusion Criteria

- History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease
- Any history or current evidence of diabetes or clinically significant abnormalities of blood glucose levels
- Any history or current evidence of inflammatory bowel disease
- History of invasive cancer within the past 5 years (excluding non-melanoma skin cancers)
- Any history of hypersensitivity to NSAIDs, COX-2 specific inhibitors, flurbiprofen, or tolbutamide
- History or presence of alcoholism or drug abuse within the past 2 years
- Use of any prescription medication (with the exception of hormonal contraceptives for females) within 1 month prior to the study
- Routine use of any over-the counter medication, including herbal supplements, within the month prior to the study. Use of any over-the-counter medication within the 5 days prior to the study
- Donation of blood within 56 days prior to the study
- Plasma donation within 7 days prior to the study
- Participation in another clinical trial within 30 days prior to the study
- Female subjects who are pregnant or lactating
- Hemoglobin < 12.0 g/dL

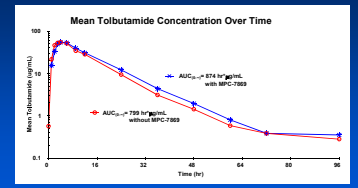
Tolbutamide PK Parameters

	Dose (mg)	MPC-7869	$t_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{0-96} (hr*μg/mL)	$CL_{ss/F}$ (mL/hr)
Tolbutamide	500	No	10.7	4	54.5	799	626
	500	Yes	11.0	4	53.9	874	572

Weight Adjusted

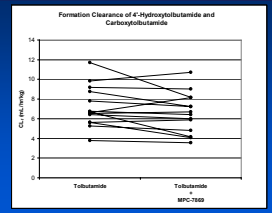
	Dose (mg/kg)	MPC-7869	$t_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/mL)	AUC_{0-96} (hr*μg/mL)	$CL_{ss/F}$ (mL/hr/kg)
Tolbutamide	7.5	No	10.7	4	54.5	799	9.4
	7.5	Yes	11.0	4	53.9	874	8.6

Effect of MPC-7869 (800 mg BID) on a Single Oral Dose of Tolbutamide: Plasma PK



- less than 10% difference between the resulting $AUC_{(0-\infty)}$

Comparison of Formation Clearances



n = 14; two subjects excluded due to apparent noncompliance

Conclusions

- PK analysis revealed less than 10% difference between the resulting $AUC_{(0-\infty)}$ for mean tolbutamide concentrations either with or without co-administration of 800 mg BID MPC-7869
- Analysis of urine revealed that the fractions metabolized via the CYP2C9 metabolic pathway were 0.70 (±0.15) and 0.72 (±0.21) in the control and MPC-7869-treated periods, respectively
- The formation clearances of tolbutamide in MPC-7869 treated and untreated states were similar
- MPC-7869 appeared safe and well-tolerated
- These data suggest that MPC-7869 will not inhibit the metabolic clearance of other drugs that are substrates for CYP2C9 and provides a rationale for the safe co-administration of such drugs
- MPC-7869 exhibits a low potential for metabolic drug interaction

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