

## Abstract

**Background:** Many antiretroviral drugs commonly used in HIV care are CYP 2D6 and 3A4 substrates. Drug interactions are problematic and carry significant clinical impacts. AMD11070 is an orally available novel antiretroviral agent "entry inhibitor," and a potent inhibitor of X4 virus. *In vitro* data indicate that it is substrate of CYP3A4, and may have a potential for inhibition of CYP2D6 and 3A4.

**Methods:** Twelve healthy subjects received a single oral dose of 5 mg MDZ and 30 mg DMP on Day 1 and Day 9. They received twice daily dosing of 200 mg AMD11070 from Day 2 through 9. PK blood samples for MDZ and DMP were collected on day 1 and 9, and AMD11070 on Day 9.

**Results:** In the presence of AMD11070, the mean  $AUC_{0-24}$  and  $C_{max}$  of DMP increased, more than doubling that in the absence of AMD 11070.  $T_{max}$  was delayed almost an hour, but the mean half-life was unchanged. Plasma  $AUC_{0-24}$  of MDZ also increased 32% (90% CI- 13- 54%) , without appreciable changes in other PK parameters . AUC changes of both drugs was linear with the rising concentration of AMD11070.

**Conclusion:** The data suggests an alteration in bioavailability due to inhibition of intestinal metabolism by AMD11070. Beneficial or deleterious effects of interaction between AMD11070 with individual CYP enzyme substrates of clinical importance should be further explored.

## Background

Despite the availability of many effective antiretroviral drugs, clinicians treatment options are still challenged by drug toxicities and the emergence of drug resistant HIV. The identification of a new class of drugs with a novel mechanism of action, durable efficacy, lack of cross-resistance with existing antiretroviral drug classes remains a continuing therapeutic need.

AMD11070 belongs to a novel class of antiretroviral entry inhibitors. It is a specific and reversible antagonist of the CXCR4 chemokine receptor and has a potent and selective activity *in vitro* to inhibit X4 viral replication by blocking fusion and viral entry into the cell. The development of a previously studied CXCR4 inhibitor, AMD3100, as an antiretroviral drug was terminated due to poor oral bioavailability and adverse effects. AMD11070 is being developed as an orally available antiretroviral drug.

In the first-in-human phase I study of AMD11070, in which healthy volunteers received either a single dose or 7 doses using a BID regimen, without a placebo control, the drug was well tolerated; mild reversible adverse effects were reported including GI complaints, headache, and asymptomatic sinus tachycardia. It is well absorbed after oral dosing and peaks in 1-2 hours. PK data from multiple dosing suggested lack of dose proportionality and a terminal half-life of 11-16 hours. A majority of subjects dosed with 200 mg BID attained plasma concentrations at or near *in vitro*  $EC_{50}$  24 hours after dosing. AMD11070, like its predecessor AMD3100, showed a dose-response for leukocytosis in healthy volunteers which may serve as a surrogate marker for CXCR4 inhibition.

AMD11070 is primarily cleared by metabolism with <1% of the oral dose appearing unchanged in the urine. *In vitro* studies indicated that it is a substrate of CYP3A4 and it shows a moderate potential for inhibition of CYP2D6 and CYP3A4. Its potential for induction seems to be low.

Because of the *in vitro* drug interaction data and since many clinically useful drugs, especially drugs used in the care of HIV-infected patients, are substrates of CYP2D6 and CYP3A4, we performed this clinical study to assess the interactions of steady-state AMD11070 with known substrates of CYP3A4 (midazolam MDZ) and CYP2D6 (dextromethorphan DMP).

Note: AMD11070 was recently placed on clinical hold by the FDA due to liver histology changes observed in longer term pre-clinical toxicity experiments. These findings are currently under investigation.

## Objective

To compare the pharmacokinetics of single dose midazolam (MDZ) and dextromethorphan (DMP) in the absence and presence of AMD11070 in healthy subjects.

## Methods

### Study Site:

Johns Hopkins Hospital, General Clinical Research Center, Baltimore, Maryland

### Study Population:

Adult healthy men and women with no active medical illness by history, physical, or laboratory evaluation

### Study Design

- Phase 1, open label, inpatient pharmacokinetic study
- Day 1:
  - single oral dose of midazolam 5 mg & dextromethorphan 30 mg
  - PK sampling:
    - MDZ: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post dose
    - DMP: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 hours post dose

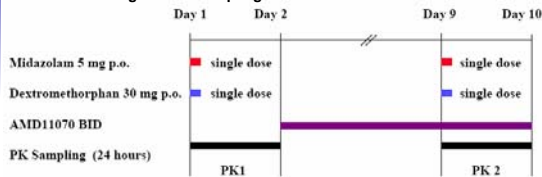
### Day 2-8:

- AMD11070 200 mg BID
- PK sampling of trough (predose) level on day 2, 3, 5, and 7

### Day 9:

- Dosing of AMD11070 200 mg BID, MDZ 5 mg x 1, DMP 30 mg x 1
- PK sampling:
  - MDZ & DMP as above
  - AMD11070: pre-AM-dose, 0.5, 1, 2, 3, 4, 8, 12 and 24 hour post dose
- Daily safety clinical evaluation and safety EKG, laboratory monitoring of hematology, chemistry and hepatic toxicity and function were done on the pre-specified days during hospital stay and two weeks after the day of first dosing

### Schema of Dosing and PK Sampling



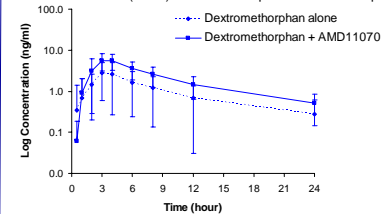
### Data Analysis

- Non-compartmental pharmacokinetic analysis was used to estimate the area under the concentration-time curve (AUC), peak concentration ( $C_{max}$ ), time to maximum concentration ( $T_{max}$ ), terminal elimination half-life ( $t_{1/2}$ ), clearance (Cl/F), and volume of distribution (V/F).
- Geometric mean ratios for drug interaction (probe drug parameters with/without AMD11070) with 90% confidence intervals were used to evaluate the magnitude of drug interactions.

## Results

- Demographics: 75% male; 75% African-American; 25% Caucasian; mean age 40 (range: 22-53)
- All subjects tolerated the study drugs well. Mild adverse effects were observed in 8 out of 12 subjects (headache, sinus tachycardia, GI discomfort, dry mouth, nasal congestion) all resolved spontaneously without medications.
- Leukocytosis was observed in all subjects.
- No liver function abnormalities were observed.

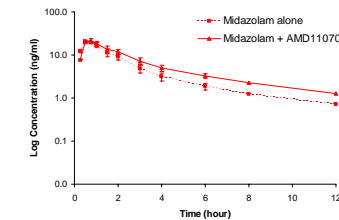
**Figure 1.** Concentration (log scale) versus time plot of dextromethorphan alone (Day 1) and in the presence of AMD11070 (Day 9). The  $C_{max}$  and AUC are 2-3 times greater in the presence of AMD11070 without a change in terminal elimination half-life (Table) as seen in the parallel terminal slopes.



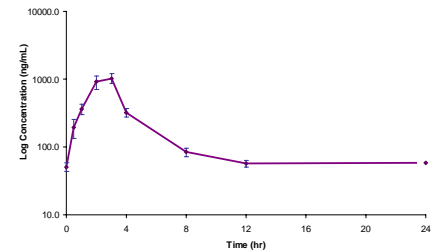
**Table.** Geometric mean ratio (90% confidence interval) day 9 –vs- day 1 pharmacokinetic parameters for dextromethorphan and midazolam. For both probe drugs, there was a statistically significant increase in both  $C_{max}$  and AUC. Since there were no changes in half-life, the nearly matched changes in clearance (Cl/F) and volume of distribution (V/F) were likely due to changes in bioavailability (F).

Parameter	Dextromethorphan	Midazolam
$AUC_{0-t}$	2.86 (2.20, 5.10)	1.33 (1.15, 1.61)
$C_{max}$	2.52 (1.99, 4.24)	1.04 (0.82, 1.50)
$T_{max}$	1.29 (1.03, 1.83)	1.17 (1.01, 1.45)
$T_{1/2}$	1.12 (0.98, 1.34)	1.12 (0.96, 1.41)
Cl/F	0.37 (0.31, 0.59)	0.72 (0.64, 0.86)
V/F	0.41 (0.35, 0.59)	0.81 (0.68, 1.08)

**Figure 2.** Concentration (log scale) versus time plot of midazolam alone and in the presence of AMD11070. Peak concentrations are similar and the terminal elimination slopes are similar, but the AUC is 33% greater in the presence of AMD11070 (Table).



**Figure 3.** Concentration versus time plot of AMD11070 on Day 9 when co-administered with MDZ 5mg and DMP 30mg. The concentration profile is similar to a previous pharmacokinetic study in healthy subjects.



## Conclusion

- AMD11070 caused a significant 2-3 fold increase in the peak concentration and AUC for CYP2D6 probe drug (dextromethorphan)
- AMD11070 caused smaller (33%), but statistically significant, changes in the CYP3A4 probe drug (midazolam) were also noted.
- Changes in the  $AUC_{0-t}$  and  $C_{max}$  of the probe drugs in concert with no change in terminal half-life and parallel changes in clearance and volume suggest an alteration in bioavailability due to inhibition of intestinal metabolism by AMD11070
- The inhibition of our probe drugs by AMD11070 may result in clinically beneficial or deleterious effects in other 2D6 and 3A4 substrate drugs which may require dose adjustment.
- Specific AMD11070 interactions with 3A4 and, especially, 2D6 substrate drugs commonly used in the care of HIV-infected patients should be studied.