A Clinical Drug-Drug Interaction Study with Midazolam to Assess the Effect of DUR-928 on CYP3A4

J. Shah[1], G. Mille[1], A. Miksztal[1], & W. Lin[1] [1]DURECT Corporation, Cupertino, CA, USA

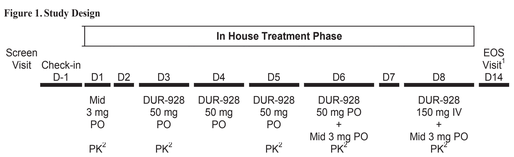
ABSTRACT

Statement of Purpose, Innovation or Hypothesis:

DUR-928 ((5-cholesten-3β,25-diol 3-sulfate (25HC3S)) is an endogenous intracellular sulfated oxysterol that has been shown to regulate lipid metabolism, inflammatory response, and cell survival. This first-in-class investigational product is being developed for the treatment of various liver and kidney diseases. A previous *in vitro* human liver microsomal study suggested the potential for DUR-928 to inhibit cytochrome P450 CYP3A4. This human drug-drug interaction (DDI) study examined the effect of DUR-928 (by either oral or intravenous infusion) on CYP3A4 using concomitant administration of oral midazolam. The study was an open-label, single sequence study in healthy human subjects (N = 17) (as shown in Figure 1).

Description of Methods and Materials:

Figure 1. Study Design



Abbreviations: D = Day, EOS = End of Study, IV = intravenous, Mid = midazolam, PK = pharmacokinetic, PO = oral, Screen = Screening.
[1] Subjects were discharged from the study center on Day 9 and returned for the EOS Visit on Day 14.
[2] Pharmacokinetic samples were collected pre-dose and after dosing with study drug.

Data and Results:

All treatments were well tolerated by study subjects throughout the duration of the trial. The treatment-emergent adverse events were mild (20/24) to moderate (4/24) in severity and resolved prior to study completion. Median time to peak plasma concentration (T_{max}) of midazolam was 0.5 hour when administered with or without DUR-928 (PO or IV). Midazolam plasma levels remained unchanged when administered alone or in combination with PO or IV DUR-928. C_{max} and area under the curve (AUC) fulfilled the no effect criteria (as shown in Table 1). Oral midazolam also had no effect on DUR-928 PK.

Table 1. Study Results

	C_{max} (ng/mL)	$AUC_{(0-\infty)}$ (ng*hr/mL)	T_{max} (hr)	T½ (hr)
Day 1 (Midazolam alone)*	16.54 (6.6)	40.5 (19.5)	0.5 [0.25 – 1.0]	3.81 (1.7)
Day 6 (Midazolam + repeat PO DUR-928)*	17.33 (9.8)	39.0 (20.0)	0.5 [0.5 – 1.0]	3.55 (1.4)
Day 8 (Midazolam + IV DUR-928)*	16.35 (7.6)	40.2 (17.1)	0.5 [0.25 – 1.5]	3.83 (1.5)
GLSM Ratio (90% CI)				
Day 6 : Day 1	0.99 (0.89, 1.10)	0.95 (0.89, 1.01)	NE	NE
Day 8 : Day 1	0.97 (0.87, 1.08)	1.01 (0.95, 1.08)	NE	NE

•Values are Mean (SD), except T_{max} presented as median [range], GLSM = Geometric least square mean, NE= Not estimated

Interpretation, Conclusion or Significance:
Co-administration with DUR-928 did not affect midazolam exposures. Based on these results, DUR-928 does not inhibit or induce CYP3A4 to a clinically meaningful extent and is not likely to markedly affect the pharmacokinetics of CYP3A4 metabolized drugs.

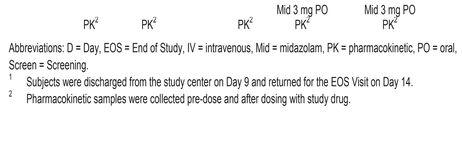
INTRODUCTION

DUR-928 ((5-cholesten-3β,25-diol 3-sulfate (25HC3S)) is a highly conserved endogenous intracellular sulfated oxysterol that has been demonstrated to play a key role in mammalian lipid metabolism, inflammatory responses and cell survival[(1)]. This first-in-class, naturally occurring sulfated oxysterol has been shown in clinical studies with patients to improve markers of liver function, and suppress markers of inflammation and cell death)[(2, 3)]. DUR-928 is being developed for the treatment of various acute or chronic liver and kidney diseases. In vitro studies conducted with human liver microsomes showed that DUR-928 is a mild inhibitor of CYP3A4. Thus, the objective of this human drug-drug interaction (DDI) study was to assess the potential effect of DUR-928, by either oral or intravenous infusion, on CYP3A4, using concomitant administration of oral midazolam[(4)].

METHODS

- This was an open-label, single sequence, single and multiple dosing study. A total of 17 healthy subjects were enrolled in and completed the study.
- Each subject received a single oral 3 mg dose of midazolam on Day 1, daily oral 50 mg of DUR-928 on Days 3 - 6. On Day 6, subjects were also co-administered a single 3 mg oral dose of midazolam. On Day 8, subjects received a 2 hour IV infusion of 150 mg DUR-928 immediately followed by a single 3-mg oral dose of midazolam. (Figure 1 for study schema)
- Blood samples for PK analysis were drawn from all subjects before dosing and for up to 24 or 26 hours after dosing on Days 1, 3, 5, 6 and 8.
- Plasma samples were processed by solid phase extraction and drugs were quantitated using a validated LC-MS/MS method. Pharmacokinetic parameters determined for midazolam and its metabolite, 1-OH midazolam, included C_{max}, T_{max}, T½, $AUC_{0\text{-last}}$, $AUC_{0-\infty}$, CL and V_z.
- All subjects were confined to the clinic until Day 9 of the study.

Figure 1. Study Design



Abbreviations: D = Day, EOS = End of Study, IV = intravenous, Mid = midazolam, PK = pharmacokinetic, PO = oral, Screen = Screening.
[1] Subjects were discharged from the study center on Day 9 and returned for the EOS Visit on Day 14.
[2] Pharmacokinetic samples were collected pre-dose and after dosing with study drug.

SUMMARY OF SUBJECT DISPOSITION

Analysis Population	Overall (N=17)
Total Number of Subjects, n (%)	17 (100 %)
Safety Population[a]	17 (100 %)
Midazolam Pharmacokinetic (PK) Population[b]	17 (100 %)
DUR-928 Pharmacokinetic (PK) Population[b]	17 (100 %)
Subjects Completed	17 (100 %)
Subjects Discontinued	0 (0 %)

Note: Percentages were based on the number of subjects overall.
[a] Safety population included all subjects who received at least 1 dose of study drug
[b]The midazolam or DUR-928 PK population included subjects with at least 1 dose of midazolam with sufficient concentration data to support accurate estimation of at least 1 primary PK parameter.

RESULTS

SUMMARY OF SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Overall (N=17)
Age (years)	
Mean (SD)	30.6 (10.5)
Minimum, Maximum	21, 55
Gender, n(%)	
Male	17 (100)
Female	0 (0)
Race, n (%)	
White	13 (76.5)
Asian	2 (11.8)
other	2 (11.8)
Ethnicity, n (%)	
Non-Hispanic / Latino	16 (94.1)
Hispanic / Latino	1 (5.9)
Height (cm)	
Mean (SD)	179.5 (9.1)
Minimum, Maximum	165, 192
Weight (kg)	
Mean (SD)	76.7 (10.1)
Minimum, Maximum	57.6, 93.1
Body Mass Index (kg/m^2)	
Mean (SD)	23.75 (2.29)
Minimum, Maximum	20.3 – 28.5

MEAN (SD) PLASMA PHARMACOKINETIC PARAMETERS OF MIDAZOLAM & 1-OH MIDAZOLAM BY TREATMENT

Parameter (unit)	Midazolam PK Parameters			1-OH Midazolam PK Parameters		
	Midazolam Alone, Day 1 (N=17)	Midazolam + PO DUR-928, Day 6 (N=17)	Midazolam + IV DUR-928, Day 8 (N=17)	Midazolam Alone, Day 1 (N=17)	Midazolam + PO DUR-928, Day 6 (N=17)	Midazolam + IV DUR-928, Day 8 (N=17)
C_{max} (ng/mL)	16.5 (6.55)	17.3 (9.77)	16.4 (7.64)	5.35 (1.99)	7.15 (3.32)	5.54 (2.07)
T_{max} (h)	0.50 (0.25 – 1.00)	0.50 (0.5 – 1.00)	0.50 (0.25 – 1.50)	0.50 (0.25 – 1.00)	0.50 (0.50 – 1.00)	0.50 (0.50 – 1.50)
T½ (h)	3.81 (1.66)	3.55 (1.35)	3.83 (1.45)	4.27 (1.96)[a]	4.21 (1.35)[a]	3.93 (1.25)[a]
$AUC_{0\text{-last}}$ (ng*h/mL)	39.2 (18.9)	37.9 (19.7)	39.0 (16.8)	11.3 (4.0)	13.4 (4.5)	11.7 (3.5)
$AUC_{0-\infty}$ (ng*h/mL)	40.5 (19.5)	39.0 (20.0)	40.2 (17.1)	12.2 (4.2)[a]	14.3 (4.7)[a]	12.4 (3.7)[a]
CL / F (L/h)	90.8 (48.4)	97.6 (58.6)	87.4 (37.1)	---	---	---
V_z / F (L)	432 (134)	426 (117)	455 (246)	---	---	---

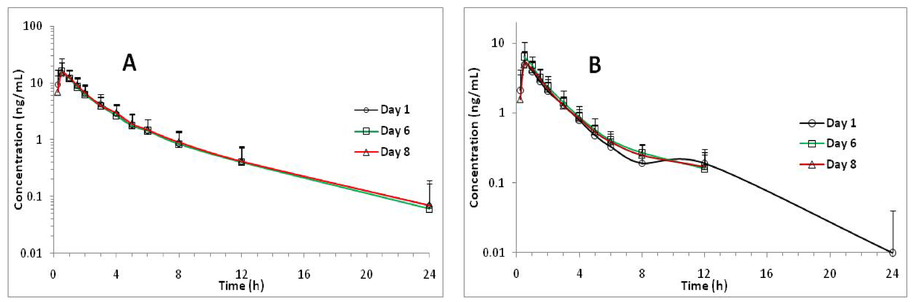
Abbreviations: SD, Standard Deviation; PK, Pharmacokinetic; h, hours.
For T_{max}, the median (minimum, maximum) values are presented. [a]N = 15

STATISTICAL COMPARISON OF MIDAZOLAM AND 1-OH MIDAZOLAM PHARMACOKINETIC PARAMETERS

Parameter	Midazolam		1-OH Midazolam	
	Ratio of Geometric Means	90% CI for the Ratio	Ratio of Geometric Means	90% CI for the Ratio
Day 6 / Day 1[1]				
C_{max}	0.991	89.0 – 110.4	1.29	112.0 – 148.4
$AUC_{0\text{-last}}$	0.950	89.0 – 101.5	1.18	111.2 – 125.8
$AUC_{0-\infty}$	0.950	89.1 – 101.3	1.18	109.7 – 126.4
Day 8 / Day 1[2]				
C_{max}	0.971	87.2 – 108.2	1.04	90.1 – 119.3
$AUC_{0\text{-last}}$	1.01	94.9 – 108.1	1.04	98.0 – 110.9
$AUC_{0-\infty}$	1.01	95.0 – 108.0	1.04	96.9 – 111.2

[1]Day 6 (oral midazolam 3 mg + oral DUR-928 50 mg) compared to Day 1 (oral midazolam 3 mg alone)
[2]Day 8 (oral midazolam 3 mg + IV DUR-928 150 mg) compared to Day 1 (oral midazolam 3 mg alone)

MEAN (SD) PLASMA CONCENTRATIONS OF MIDAZOLAM (A) & 1-OH MIDAZOLAM (B) VERSUS TIME ON SEMILOGARITHMIC SCALE



Day 1 – Oral Midazolam Alone; Day 6 – Oral Midazolam + Oral DUR-928; Day 8 – Oral Midazolam + IV DUR-928

CONCLUSIONS

▪ Pharmacokinetics

- DUR-928, whether daily oral dosing or IV infusion, did not affect the C_{max} and $AUC_{0-\infty}$ of co-administered oral midazolam, nor did it affect the $AUC_{0-\infty}$ of 1-OH midazolam. There was minimal effect indicated on the C_{max} of 1-OH midazolam.
- No accumulation of DUR-928 was observed upon repeat oral dosing.
- No evidence of oral 3 mg midazolam affecting PK parameters of DUR-928.
- DUR-928 did not appear to have a clinically significant effect on CYP3A4 at doses studied, and it may be co-administered with drugs that are primarily CYP3A4 substrates.

▪Safety

- All subjects tolerated the treatments generally well throughout this study.
- All reported adverse events were mild to moderate in severity with no SAEs or TEAEs leading to study discontinuation.
- No treatment related trends were observed with regard to OAA/S[1] scores or concomitant medication use.

[1] Observer's Assessment of Alertness/Sedation

REFERENCES

1. Ren and Ning, *Am J Physiol Endocrinol Metab* 306:E123–E130, 2014.
2. Kemp W, et al. J Hepatology, 2017; 66 (1), S596.
3. Kim M J, et al. AASLD: Emerging Trends in NAFLD Meeting , 2017.
4. U.S. Department of Health and Human Services, FDA CDER. Draft 2017. Guidance for Industry: Clinical Drug Interaction Studies – Study Design, Data Analysis & Clinical Implications

Meeting of the American College of Clinical Pharmacology, ***Bethesda, Maryland, September 23-25, 2018***