Safety, Tolerability, and Pharmacokinetics of MZE829, an APOL1 Inhibitor, in Healthy Adult Volunteers

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Introduction

Genetic gain of function variants of apolipoprotein L1 (APOL1) directly damages podocytes and are associated with an increased risk of proteinuric chronic kidney disease and disease progression in individuals of West African ancestry. MZE829 is an orally bioavailable small molecule and highly potent inhibitor of APOL1 which is currently under investigation for the treatment of APOL1 kidney disease (AKD). Previously we presented that oral administration of a small molecule APOL1 inhibitor, robustly blocked APOL1 lytic activity, reduced APOL1-mediated cytotoxicity in kidney cells and reversed established IFNγ–induced albuminuria in a mouse model of AKD.

Study Design and Objectives

Study design: Phase 1 randomized, blinded, placebo-controlled trial of single and multiple ascending doses of MZE829 and drug-drug interactions in healthy participants ages 18 to 60 years

Study objectives:

- Primary: To evaluate the safety and tolerability of single and multiple ascending oral doses of MZE829 in healthy volunteers
- Secondary:
  - To evaluate the PK following single ascending oral doses of MZE829
  - To evaluate the food effect of a single dose of MZE829
  - To evaluate the PK following multiple ascending oral doses of MZE829
- Exploratory: To explore potential drug-drug interactions with itraconazole (SAD) and midazolam (MAD)

Figure 1: Phase 1 study schematic

Results

Study population diverse in age, sex, race, and ethnicity

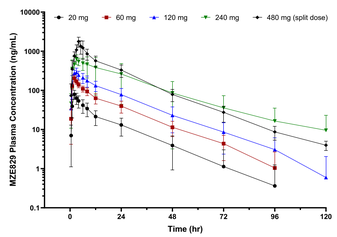
Table 1: Demographics	MZE829 N=87	Placebo N=24	Total N=111
Age, years			
Mean	37	38	37
Median	36	36	36
Min, Max	19, 60	23,60	19,60
Sex, n (%)			
Female	43 (49)	12 (50)	55 (50)
Male	44 (51)	12 (50)	56 (50)
Race, n (%)			
American Indian or Alaska Native	1 (1)	0	1 (1)
Asian	2 (2)	1 (4)	3 (3)
Black or African American	25 (29)	8 (33)	33 (30)
Native Hawaiian or Other Pacific Islander	2 (2)	1 (4)	3 (3)
White	55 (63)	13 (54)	68 (61)
Multi-racial	2 (2)	1 (4)	3 (3)
Ethnicity, n (%)			
Hispanic or Latino	40 (46)	5 (21)	45 (40)
Not Hispanic or Latino	47 (54)	19 (79)	66 (60)

MZE829 safe and generally well tolerated at single doses up to 480 mg and multiple doses up to 350 mg QD

- Vital signs, laboratory studies, ECGs, and clinical examination: No clinically relevant or dose-dependent changes
- MZE829 well-tolerated at single doses up to 480 mg and multiple doses up to 350 mg QD x 7 days
  - All treatment-related AEs (TRAEs) reported as mild
  - Proportion of subjects with any TRAE: MZE829 vs placebo, 20% vs 13%
  - TRAE reported in ≥3 subjects: headache, 20% vs 4%
- Dose-related transient headache, nausea, and vomiting observed at doses estimated to be supratherapeutic based on a mouse model of AKD
  - 480 mg split-dose: Mild TRAEs observed in 4 of 6 subjects
    - Headache (n=3), nausea (n=3), and vomiting (n=3)
  - 480 mg QD: Mild and moderate TRAEs observed in 5 of 6 subjects:
    - Headache (n=2, moderate; n=2, mild), vomiting (n=1, moderate), and nausea (n=4, mild)
  - Dosing stopped after 2 doses in 480 mg QD cohort
- No severe AEs or SAEs reported

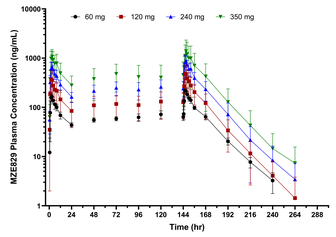
MZE829 has linear PK with dose proportional increases and relatively low PK variability (10-40%)

Figure 2: Single ascending doses



Note: Single doses up to 480 mg were also evaluated in the study. Due to inconsistent exposures, these data are not shown here. Evaluation of the same dose level administrated as split dose (2 hours apart) as well Day 1 exposures at 480 mg MAD cohort suggest the low exposures observed in the 480 mg single dose cohort were erroneous. LLOQ=2ng/ml. n=6/cohort

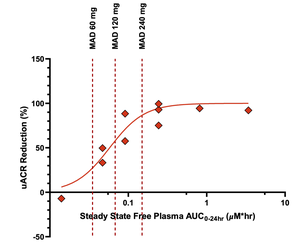
Figure 3: Multiple ascending doses



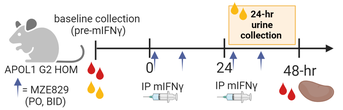
Note: Dosing was discontinued in 480 mg QD cohort after second dose. These data are not shown here. LLOQ=2ng/ml. n=6/cohort

Observed human exposures fall within efficacious range for proteinuria reduction in a mouse model of AKD

Figure 4: Exposure-response in mouse model of AKD



Note: Human exposures shown as dotted red lines are those at steady-state (Day 7) in MAD cohorts



MZE829 is moderately sensitive to strong CYP3A inhibition by itraconazole. MZE829 is not an inhibitor of CYP3A. No clinically significant interactions with MZE829 predicted with cyclosporine or tacrolimus.

Figure 6: Effect of itraconazole on MZE829 GLSM ratio (90%CI)

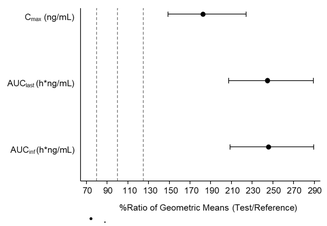
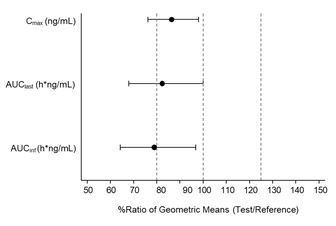
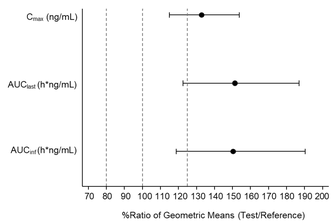


Figure 7: Effect of MZE829 on midazolam GLSM ratio (90%CI).



Food (high-fat meal) increased MZE829 exposures by 33% to 50%

Figure 5: Comparison of fed to fasted administration GLSM ratio (90%CI)



Conclusions

MZE829 is a potent, selective, small molecule APOL1 inhibitor. Phase 1 evaluation in healthy participants demonstrated that safe and well-tolerated doses of MZE829 achieve exposures through the range estimated to be efficacious based on a mouse model of AKD.

A MZE829 phase 2 global clinical trial will enroll proteinuric CKD patients with high-risk APOL1 variants to demonstrate clinical proof of concept for proteinuria reduction.