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Impact of Food on the PK and Tolerability of RAP-219 in Healthy Volunteers

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Background

- TARPγ8, a transmembrane AMPA receptor regulatory protein (TARP), provides a novel target for seizure control due to its enriched expression in the hippocampus, cortex, and amygdala with minimal expression in the hindbrain[1]
  - AMPA receptor inhibition in the hindbrain (cerebellum) is associated with CNS adverse events (AEs) such as gait disturbances and somnolence[2]
- RAP-219 is a highly potent, selective negative allosteric modulator of AMPA receptors expressing TARPγ8, thereby offering a precision approach towards AMPA receptor inhibition
- Food can affect the rate and extent of antiseizure medication (ASM) absorption, adding complexity for patients establishing an optimal daily regimen,[3] particularly if the patient is using multiple ASMs

Objective

- Here, we describe the initial evaluation of the impact of food on the pharmacokinetics (PK) and tolerability of RAP-219 as part of a Phase 1 single ascending dose (SAD) trial

Methods

- Six healthy subjects (18-55 y) were enrolled in a food-effect cohort of the open-label SAD study
  - Due to the long terminal elimination half-life (202-362 h, or approximately 8-14 days), which introduces an issue with washout, a parallel cohort design was selected
  - Key demographics in the food-effect cohort were matched to those in the corresponding fasted cohort (SAD trial Cohort 3, single dose of 1 mg RAP-219)
    - Age (mean±10 y), sex (equal number of females), body weight (mean±10%), and race (equal number of non-White subjects)
- Subjects were given a single oral dose of 1 mg RAP-219 on Day 1 30 min after the start of a standardized high-fat, high-calorie breakfast (56 g fat, 65 g carbohydrates, 41 g protein, and 948 kcal)
  - The dose was selected based on the tolerability and PK determined during the fasted SAD trial
  - Blood samples were collected pre-dose and over 13 timepoints post-dose (15 min to 144 h)
  - Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the serum concentration-time curve from time 0 to the last timepoint (AUC_{0-144}), and terminal half-life ($t_{1/2}$) were calculated
- The effect of a high-fat meal was assessed using *ln*-transformed C_{max} and AUC_{0-144} values in an ANOVA model (treatment period as a fixed effect) via 2 one-sided tests (α=0.05)
  - The ANOVA model compared the food-effect cohort (fed, single-dose 1 mg RAP-219) to Cohort 3 (fasted, single-dose 1 mg RAP-219) of the SAD trial
  - Geometric mean ratios (90% CI) from the ANOVA model were determined; food effect on RAP-219 PK parameters was determined by comparing the 90% CI to standard predefined limits (80%-125%)
  - T_{max} values under fasted and fed conditions were assessed using the Wilcoxon rank sum test (α=0.05)
- Treatment-emergent AEs (TEAEs) and serious AEs were recorded to assess tolerability
  - TEAE severity was evaluated using the NCI-CTCAE v5.0 scale
    - Grade 1 (mild) to Grade 5 (death related to AE)

Results

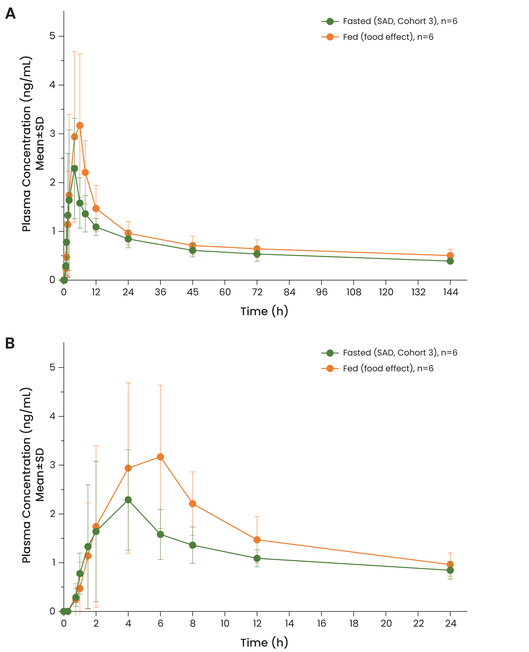
Table 1. Demographics of Healthy Fasted and Fed Subjects Treated with a Single Dose of 1 mg RAP-219

	Fasted (SAD, Cohort 3) n=6	Fed[a] (Food-Effect Cohort) n=6
Age, years, mean±SD	41.3±11.5	34.7±4.6
Sex, female, n (%)	1 (16.7)	1 (16.7)
Race, n (%)		
Black or African American	2 (33.3)	3 (50.0)
White	3 (50.0)	3 (50.0)
Multiple	1 (16.7)	0
Body weight, kg, mean±SD	72.4±9.4	73.4±4.2

[a]Subjects were provided a high-fat meal containing 56 g fat, 65 g carbohydrates, 41 g protein, and 948 kcal.
SAD – single ascending dose.

- The absorption profile of RAP-219 shows a possible moderate food effect
- Compared to subjects in the fasted condition, subjects given a high-calorie, high-fat meal exhibited a 42% increase in C_{max} and a 25% increase in AUC_{0-144}, along with a slight delay in the median t_{max} of 1 h (**Figure 1** and **Table 2**)

Figure 1. Concentration-Time Data for a Single Dose of 1 mg RAP-219 in Fasted and Fed Healthy Subjects at **A.** 144 h and **B.** 24 h



Fasted and fed subjects were administered a single dose of 1 mg RAP-219.
C_{max} – maximum observed plasma concentration; **SAD** – single ascending dose; t_{max} – time at which maximum observed plasma concentration is achieved.

Table 2. PK Parameters (Mean±SD) and ANOVA Food-Effect Analysis of a Single Dose of 1 mg RAP-219 in Healthy Fasted and Fed Subjects

	Fasted (SAD, Cohort 3) n=6	Fed (Food-Effect Cohort) n=6
t_{max}[a], h	4.0±8.4	5.0±2.1
C_{max}, ng/mL	2.7±1.3	3.6±1.2
Geometric mean	2.4	3.4
Geometric mean ratio (90% CI)	141.8 (89.4, 225.1)	
AUC_{0-144}, ng*h/mL	92.7±14.0	119±24.6
Geometric mean	91.8	115.0
Geometric mean ratio (90% CI)	125.0 (102.3, 152.8)	
$t_{1/2}$, h	341±405	228±162

[a]Median values presented for t_{max}.
ANOVA – analysis of variance; AUC_{0-144} – area under the plasma concentration-time curve from time 0 to 144h post-dose (last measurable timepoint); C_{max} – maximum observed plasma concentration; **PK** – pharmacokinetic; **SAD** – single ascending dose; $t_{1/2}$ – half-life; t_{max} – time at which maximum observed plasma concentration is achieved.

Tolerability

- There was a single Grade 1 TEAE each in the fasted and fed 1 mg groups (fasted: tension headache; fed: confusional state)
- There were no clinically significant changes in laboratory values, electrocardiogram (ECG) parameters, or vital signs in either group

Conclusions

- A high-fat, high-calorie meal resulted in a moderate increase in RAP-219 C_{max} and AUC_{0-144} as well as a slight delay in RAP-219 absorption under fed vs fasted conditions
- Data from this study suggest that food will not have a clinically meaningful impact on RAP-219 PK, and therefore, RAP-219 will be dosed without regard to meal time in the planned Phase 2 studies
- A definitive study is planned to fully characterize the effect of food on RAP-219 PK

References
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