PF256

Evaluation of food effect on pharmacokinetics of ivosidenib (AG-120), an oral, potent, targeted, small molecule inhibitor of mutant IDH1, in healthy subjects

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BACKGROUND

- Somatic mutations in the metabolic enzyme isocitrate dehydrogenase 1 (IDH1) result in gain-of-function activity, catalyzing the reduction of α-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (2-HG).[1]
- 2-HG accumulation results in inhibition of α-KG–dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.[2-4]
- Mutant IDH1 (mIDH1) has been identified in multiple types of solid tumors and hematologic malignancies.
- Ivosidenib (AG-120) is an oral, potent, targeted, small-molecule mIDH1 inhibitor that has the potential to be the foundation of treatment for mIDH1-driven cancers, and is under evaluation in multiple clinical studies of mIDH1 malignancies.
- Ivosidenib has been well tolerated in all patient populations studied.[5-9]
- In a phase 1 study, ivosidenib treatment resulted in an overall response rate of 42%, a complete remission (CR) rate of 24%, and a CR+CR with partial hematologic recovery rate of 32% in patients with mIDH1 relapsed or refractory acute myeloid leukemia.
  - See presentation S1560 Pollyea DA et al., Sunday, 17 June, 08:00–08:15.
- Ivosidenib has also shown activity in patients with solid tumors, including advanced cholangiocarcinoma,[7] chondrosarcoma,[8] and glioma.[9]
- As ivosidenib is orally administered, it is important to understand the effect of food on the pharmacokinetic (PK) characteristics of ivosidenib and to determine the relative bioavailability of ivosidenib in relation to meal consumption; this is essential for optimal dosing in future clinical trials.

OBJECTIVE

- To investigate the effect of a high-fat, high-calorie meal on the PK of ivosidenib in healthy subjects.

METHODS

Design

- This was a phase 1, open-label, randomized, two-period crossover study to evaluate the effect of food on ivosidenib PK following administration of a single oral dose of 500 mg in healthy subjects aged 18–55 years (ClinicalTrials.gov NCT02579707).
- Safety and tolerability were also evaluated for a single oral dose of 500 mg ivosidenib.
- The study was conducted according to the United States Food and Drug Administration (FDA) 2002 Guidance for Industry “Food-Effect Bioavailability and Fed Bioequivalence Studies”.

Treatment

- Treatments A and B, each comprising a single oral dose of 500 mg ivosidenib, were administered as shown in **Table 1**.
  - A (fasted): two 250 mg tablets administered after an overnight fast (~10 hr).
  - B (fed): two 250 mg tablets administered after a standardized high-fat breakfast, consumed within 30 min prior to ivosidenib dosing.
- The standardized FDA high-fat content meal contains the equivalent of ~150 protein calories, ~250 carbohydrate calories, and ~500–600 fat calories, and comprises two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes (fried with butter), and eight ounces (240 mL) of whole milk.
- Of the 30 subjects enrolled, 15 were randomized to sequence AB and 15 were randomized to sequence BA.

Table 1. Treatment sequence

Sequence	Period 1	Washout period	Period 2
AB	500 mg ivosidenib (fasted)	≥25 days	500 mg ivosidenib (fed)
BA	500 mg ivosidenib (fed)	≥25 days	500 mg ivosidenib (fasted)

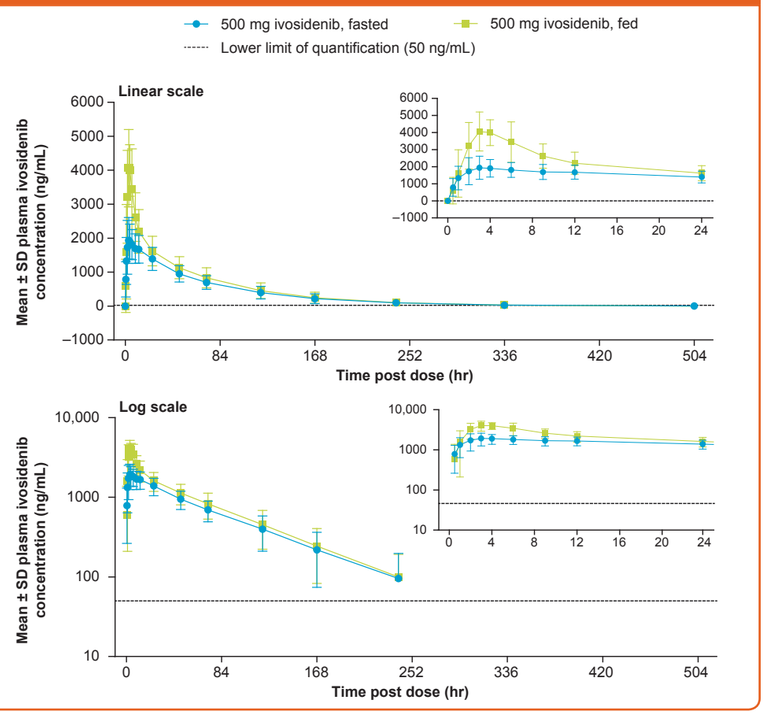
Assessments

- Blood samples for the analysis of ivosidenib concentrations were collected pre dose and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 120, 168, 240, 336, and 504 hr post dose.
- Plasma concentrations of ivosidenib were determined using a validated liquid chromatography with tandem mass spectrometry method.
- PK parameters were calculated using WinNonlin (Pharsight Corporation, Version 6.2.1).
- Linear mixed model analysis was performed on natural logarithm-transformed maximum observed concentration (C_{max}), area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), and area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$). The analyses were performed using the SAS® MIXED procedure.
- The geometric mean ratios (fasted vs fed) and their associated 90% CIs for C_{max} and AUCs were calculated to determine whether food had an effect on the PK of ivosidenib.
- Inter-subject variability was determined using the geometric coefficient of variation percent (CV%).
- Incidence of adverse events and serious adverse events was assessed.

RESULTS

- Following administration in the high-fat fed and fasted conditions, 500 mg ivosidenib was readily absorbed, with similar median time to C_{max} (T_{max}) values of 3.00 and 3.03 hr post dose, respectively (**Figure 1**).
- After reaching C_{max}, plasma concentrations slowly declined in a multiphasic manner, with similar mean apparent terminal elimination half-life ($t_{1/2}$) values of 53.2 hr in the fed condition and 55.4 hr in the fasted condition.
- A large increase in C_{max} was observed in the fed compared with the fasted condition, while the extent of exposure (assessed by mean AUC_{0-t} and $AUC_{0-\infty}$) was higher following dosing in the fed versus the fasted condition (**Table 2**).

Figure 1. Mean (± SD) plasma concentrations of ivosidenib over time following a single 500 mg oral dose under fasted and fed conditions



- The inter-subject variability for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} was similar and moderate for both the fed and fasted conditions, with CV% values ranging from 31.1% to 31.6% for AUC, and from 21.3% to 24.3% for C_{max}.
- A single oral dose of 500 mg ivosidenib administered in the fed and fasted conditions appeared to be safe and well tolerated in healthy subjects.

Table 2. Plasma PK parameters of ivosidenib following a single oral dose of 500 mg ivosidenib under fasted and fed conditions

PK parameter	500 mg ivosidenib, fasted n=29	500 mg ivosidenib, fed n=27
AUC_{0-t} (hr·ng/mL)[a]	136,000 (31.6)	166,000 (31.2)
$AUC_{0-\infty}$ (hr·ng/mL)[a]	143,000 (31.1)	174,000 (31.2)
C_{max} (ng/mL)[a]	2270 (21.3)	4490 (24.3)
T_{max} (hr)[b]	3.03 (1.00–24.00)	3.00 (1.00–6.00)
$t_{1/2}$ (hr)[c]	55.4 (20.5)	53.2 (18.3)

[a]Geometric mean (CV%)
[b]Median (min–max)
[c]Arithmetic mean (SD)
AUC_{0-t} = area under the plasma concentration-time curve from Hour 0 up to the last measureable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve extrapolated to infinity; C_{max} = maximum observed concentration; PK = pharmacokinetic; $t_{½}$ = apparent terminal elimination half-life; T_{max} = time of the maximum concentration

- An increase of ~2-fold in mean C_{max} was observed.
- The lower limit of the 90% CIs for the C_{max} geometric least square (LS) means ratio (178.7, 218.9) was above 100 when ivosidenib was administered following a high-fat meal compared with the fasted condition (**Table 3**).
- The extent of exposure increased by 25.6% and 24.3% as assessed by AUC_{0-t} and $AUC_{0-\infty}$, respectively.
- The lower limit of the 90% CIs for the geometric LS-means ratios for AUC_{0-t} (117.2, 134.6) and $AUC_{0-\infty}$ (116.3, 132.9) was above 100 when ivosidenib was administered following a high-fat meal compared with the fasted condition.

Table 3. Statistical summary of the effect of food on ivosidenib PK (n=27)

Comparison	Parameter	Geometric mean ratio (%)	90% CI (%)
Ivosidenib administered in the fed condition (test) versus in the fasted condition (reference)	C_{max}	197.8	178.7, 218.9
	AUC_{0-t}	125.6	117.2, 134.6
	$AUC_{0-\infty}$	124.3	116.3, 132.9

CONCLUSIONS

- Consumption of a high-fat meal prior to dosing had an effect on ivosidenib exposure, with a ~2-fold increase in C_{max} and a ~25% increase in AUC.
- It is recommended that ivosidenib be administered with or without food; however, high-fat meals at time of dosing should be avoided.

Disclosures

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References

1. Dang L et al. *Nature* 2009;462:739-44. **2.** Lu C et al. *Nature* 2012;483:474-8. **3.** Saha SK et al. *Nature* 2014;513:110-4. **4.** Xu W et al. *Cancer Cell* 2011;19:17-30. **5.** DiNardo CD et al. *Blood* 2017;130(Suppl 1):A725. **6.** Burris H et al. *Mol Cancer Ther* 2015;14(12[Suppl 2]):Abstr PL04-05. **7.** Lowery MA et al. *2017 ASCO Annual Meeting:* P4015. **8.** Tap W et al. *CTOS 2016:* P1-138. **9.** Mellinghoff I et al. *SNO 2017:* ACTR-46.

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