PIII-011

Relationship of ivosidenib (AG-120) plasma concentration to heart rate–corrected QT interval (QTc) in patients with IDH1-mutant advanced hematologic malignancies

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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 alpha-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxyglutarate (2-HG).[1]
- 2-HG accumulation results in the 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 hematologic malignancies and solid tumors.
- Ivosidenib (AG-120) is an oral, potent, targeted inhibitor of mIDH1[5] that is approved in the US for the treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test.[6]
- Ivosidenib is also being evaluated in multiple other mIDH1 tumor types, including advanced solid tumors such as cholangiocarcinoma, chondrosarcoma, and glioma.
- Prolongation of the QT interval on electrocardiogram (ECG) has previously been identified as an adverse event of special interest for ivosidenib.[7]
- Here, we investigate the relationship between ivosidenib exposure and heart rate–corrected QT interval (QTc) in patients with mIDH1 advanced hematologic malignancies.

OBJECTIVES

- To characterize the relationship between ivosidenib plasma concentration and change in QTc (ΔQTc).
- To predict the ivosidenib-associated ΔQTc at relevant concentrations in patients with mIDH1 advanced hematologic malignancies.

METHODS

Data included

- The relationship between ivosidenib concentration and QTc was evaluated on the basis of data from three phase 1 studies (**Table 1**).

Table 1. Studies included in this analysis

Study	Design	Treatment	Population	ClinicalTrials.gov registry number
AG120-C-001	Phase 1, open-label, dose escalation and expansion study	Daily oral doses of ivosidenib 200–1200 mg, in 28-day cycles[a]	Patients with mIDH1 advanced hematologic malignancies	NCT02074839
AG120-C-002	Phase 1, open-label, dose escalation and expansion study	Daily oral doses of ivosidenib 200–1200 mg, in 28-day cycles[a]	Patients with mIDH1 advanced solid tumors, including glioma	NCT02073994
AG120-C-004	Randomized, two-period crossover food-effect study	Single oral dose of ivosidenib 500 mg or 1000 mg	Healthy subjects	NCT02579707

[a]500 mg once daily (QD) was selected as the recommended ivosidenib dose for the expansion phase

- Single and triplicate 12-lead ECGs were collected pre dose and at 0.5–8 hr post dose in studies AG120-C-001 and AG120-C-002, and at 1, 2, 4, and 24 hr post dose in study AG120-C-004.
- Concurrent samples for the assessment of ivosidenib plasma concentrations were obtained at the same nominal time points.
- A full QT analysis dataset was created that contained all evaluable baseline ECG measurements and postbaseline time-matched concentration-QT interval measurements.
- A triplicate-only dataset (excluding single and duplicate ECG measurements; "triplicate dataset") was used for the primary analysis to provide maximum precision.
- The Bazett and Fridericia methods were compared for their ability to correct for the effect of heart rate on QT interval.
  - Linear regression analyses of baseline QT interval, Bazett-corrected QT interval (QTcB), and Fridericia-corrected QT interval (QTcF) versus the RR interval were performed, and the method providing the slope closest to 0 was selected.

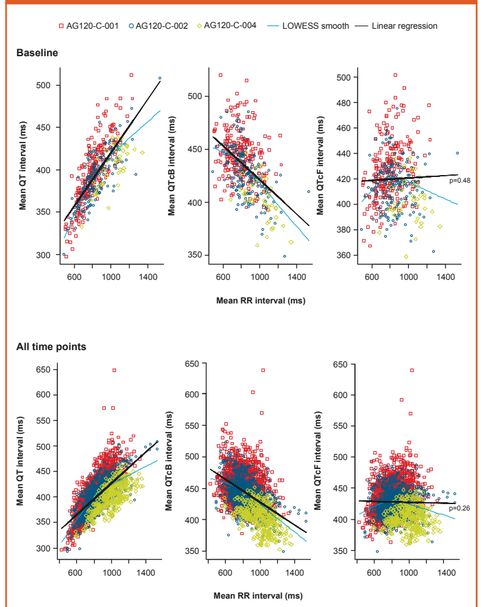
Modeling

- R version 3.2.4 (R Foundation, Vienna, Austria) was used for all data processing and analysis.
- The modeled endpoint was Fridericia-corrected ΔQTc (ΔQTcF).
- Linear mixed-effects models were used to quantify the concentration-ΔQTcF relationship.
- The intercept and slope were modeled as population mean values with additive random between-subject variability.
- Covariates were tested as additions to the intercept term in a standard stepwise forward selection–backward elimination search strategy.
- Tested covariates included baseline demographics (age, sex, race, body weight); baseline QTcF; electrolytes (calcium, potassium, magnesium); study effects; healthy subjects versus patients with cancer; baseline tumor type; medications with known risk of prolonging QT interval; medications with known risk for torsades de pointes; cardiac disorder at baseline.
  - Missing covariate observations (e.g. electrolytes) were imputed using one of the following methods, in order of priority: (1) last observation carried forward; (2) next observation carried backward; or (3) the missing value was imputed as the overall mean across nonmissing observations for all subjects, or across nonmissing baseline values for a baseline-only covariate (e.g. body weight).
- The relative performance of the models was evaluated using the likelihood ratio test at the 0.05 significance level, as well as by assessing the precision of the parameter estimates.
- The final model was used to predict the expected QTc prolongation and 90% CI for the geometric mean maximum ivosidenib plasma concentration (C_{max}) at various QD doses.

RESULTS

- **Figure 1** shows the performance of the Bazett and Fridericia QT correction methods in the full QT dataset.
  - Among QT, QTcB, and QTcF, the slope of the regression line became nonsignificant only for the Fridericia correction (p=0.48 for baseline only, p=0.26 for all time points).
  - Therefore, the Fridericia correction was selected for the analysis.
- A total of 2377 triplicate ECG measurements with time-matched concentration samples from 314 subjects (from all three studies) were included in the primary analysis.
  - This corresponds to ~85% of the full QT dataset.

Figure 1. QT, QTcB, and QTcF versus RR interval[a] at baseline and all time points (full QT dataset)



Each symbol represents the average of one to three measurements from a single subject
[a]RR interval on ECG, the inverse of heart rate, calculated as 60,000 ms / heart rate in beats per min, averaged over the one, two, or three observations per record
LOWESS = locally weighted polynomial regression for scatterplot smoothing

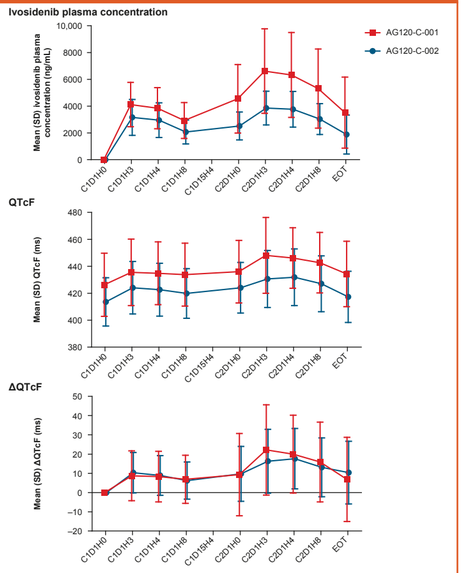
- The baseline characteristics for the triplicate dataset are summarized in **Table 2**.
- Graphical inspection of the mean profiles for ivosidenib plasma concentration and QTcF over time showed no evidence of hysteresis; i.e. when the concentration changed substantially between visits, QTcF changed in the same direction without delay (**Figure 2**).

Table 2. Baseline characteristics by study and dose group in the triplicate dataset

	AG120-C-001 500 mg QD (n=171)	AG120-C-002 500 mg QD (n=107)	AG120-C-004		All 3 studies All doses (N=314)
			500 mg QD (n=30)	1000 mg QD (n=6)	
QTcF, mean (SD), ms	426.3 (23.5)	413.6 (18.0)	402.1 (18.1)	403.6 (16.6)	419.2 (22.7)
Age, mean (SD), years	67.0 (13.0)	51.2 (13.2)	34.9 (11.5)	31.0 (5.2)	57.8 (17.0)
Weight, mean (SD), kg	76.8 (18.2)	79.3 (19.1)	74.9 (12.2)	74.4 (10.5)	77.4 (17.9)
Men/women, %	53.8/46.2	47.7/52.3	56.7/43.3	33.3/66.7	51.6/48.4
White race, %	64.9	74.8	60.0	50.0	67.5
Tumor type, %					
R/R AML	79.5	0	0	0	43.3
Myelodysplastic syndrome	5.3	0	0	0	2.9
Cholangiocarcinoma	0	45.8	0	0	15.6
Chondrosarcoma	0	7.5	0	0	2.5
Glioma	0	43.0	0	0	14.6
Other/none	15.2	3.7	100	100	21.0
Baseline cardiac disorder, %	33.3	11.2	NA	NA	NA
On medication with known QT risk, %	75.4	25.2	NA	NA	NA
>1 medication category with QT risk, %	36.8	0	NA	NA	NA
On medication with known TdP risk, %[a]	64.3	27.1	NA	NA	NA
Electrolytes, mean (SD), mmol/L					
Calcium	2.24 (0.149)	2.34 (0.166)	2.39 (0.074)	2.41 (0.086)	2.29 (0.160)
Albumin-corrected calcium	2.32 (0.106)	2.33 (0.177)	2.29 (0.042)	2.31 (0.061)	2.32 (0.131)
Potassium	4.00 (0.414)	4.02 (0.396)	4.32 (0.338)	4.32 (0.172)	4.05 (0.409)
Magnesium	0.804 (0.101)	0.817 (0.081)	0.827 (0.064)	0.827 (0.031)	0.811 (0.091)

[a]Can exceed the proportion of patients on medication with known QT risk, owing to differing definitions
NA = not available; TdP = torsades de pointes (type of abnormal heart rhythm)

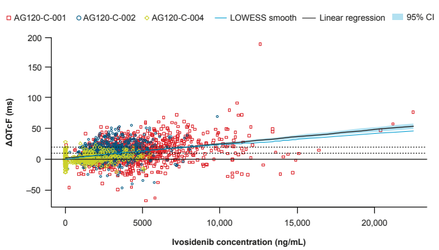
Figure 2: Mean (SD) ivosidenib plasma concentration, QTcF, and ΔQTcF over time in studies AG120-C-001 and AG120-C-002 (triplicate dataset)



C = Cycle; D = Day; EOT = end of treatment; H = Hour

- A positive and approximately linear relationship was observed between ΔQTcF and ivosidenib plasma concentration (**Figure 3**).

Figure 3. Relationship between ΔQTcF and ivosidenib plasma concentration in the triplicate dataset



Each symbol represents the average of three measurements from a single subject. Dotted lines denote the 10 ms and 20 ms thresholds

- **Table 3** provides the parameter estimates for the final primary model.
  - The relationship between ivosidenib concentration and ΔQTcF was best described by a linear model with additive random effects on the intercept and slope parameters and a study effect on the slope.
  - Five covariates were found to be significant in forward selection–backward elimination: (1) baseline QTcF; (2) age; (3) corrected calcium 5-day average; (4) a flag for magnesium (1 if greater than the covariate mean and 0 otherwise); and (5) a flag for concomitant medications with known risk for prolonging QT interval (1 if yes, 0 if no).
  - Final model:
    $\Delta QTcF = Intercept + Slope_{AG120\text{-}C\text{-}001} \times Conc_{AG120\text{-}C\text{-}001} + Slope_{AG120\text{-}C\text{-}002} \times Conc_{AG120\text{-}C\text{-}002} + Slope_{AG120\text{-}C\text{-}004} \times Conc_{AG120\text{-}C\text{-}004} + Cov_1 + Cov_2 + Cov_3 + Cov_4 + Cov_5 + residual\ error\ (\varepsilon)$,
    where Covariate$_n$ = Covariate coefficient$_n$ [shown in **Table 3**] × (Covariate - mean)$_n$.
    Conc = concentration; Cov = covariate; in case of flag, covariate "mean" = the proportion of the sample population that is flagged
  - In the hematologic malignancy population, QTcF was predicted to increase by 0.00258 ms with every 1 ng/mL increase in ivosidenib concentration (RSE=9.5%).

Table 3. Model parameter estimates for the primary final model (triplicate dataset)

	Estimate	SE	RSE, %	95% CI	p-value
Fixed effects					
Intercept, ms	0.260	0.414	159	(–0.550, 1.07)	0.529
Ivosidenib concentration-ΔQTcF slope, ms/(ng/mL)					
Study AG120-C-001	0.00258	0.000245	9.50	(0.00210, 0.00306)	<0.001
Study AG120-C-002	0.00379	0.000328	8.65	(0.00315, 0.00444)	<0.001
Study AG120-C-004	0.00120	0.000585	48.8	(5.62e-5, 0.00235)	0.040
Baseline QTcF, mean, ms/ms	–0.108	0.0180	16.7	(–0.143, –0.0728)	<0.001
Age, mean, ms/years	0.116	0.0245	21.1	(0.0684, 0.165)	<0.001
Albumin-corrected calcium 5-day average, mean, ms/(mmol/L)	–10.7	2.64	24.7	(–15.9, –5.55)	<0.001
Flag for subjects on medication with known QT prolongation risk, mean, ms	–1.76	0.734	41.7	(–3.20, –0.326)	0.016
Flag for subjects with magnesium > mean value, mean, ms/(mmol/L)	–1.23	0.568	46.2	(–2.34, –0.114)	0.031
Between-subject variability					
Intercept SD, ms	2.75	0.851	31.0	(1.56, 4.86)	NC
Concentration SD in all studies, ms	0.00269	0.000211	7.83	(0.00231, 0.00313)	NC
Intercept-concentration correlation	–0.00220	NC	NC	(–0.540, 0.537)	NC
Residual (unexplained) variability					
σ, ms	9.51	0.156	1.64	(9.21, 9.82)	NC

NC = could not be calculated; RSE = relative standard error; SE = standard error; σ = residual error standard deviation

- The final primary model was used to quantify the magnitude of the mean ΔQTc at the geometric mean C_{max} values across subjects on various dose levels in study AG120-C-001 (**Table 4**).
  - At the steady-state geometric mean C_{max} of 6551 ng/mL for the recommended clinical dose of 500 mg QD in patients with hematologic malignancies, a ΔQTcF of 16.1 ms (90% CI 13.3, 18.9 ms) was predicted in patients with R/R AML.
  - At 500 mg QD, the upper bound of 90% CI was <20 ms for patients with hematologic malignancies overall as well as for the subpopulation with R/R AML.

Table 4. Projections of mean (90% CI) ΔQTcF at various doses of ivosidenib in study AG120-C-001

Dose	C_{max}[a] ng/mL	ΔQTcF, mean (90% CI), ms	
		Primary model	R/R AML only
250 mg QD	4600	12.1 (10.4, 13.9)	11.5 (9.5, 13.4)
300 mg QD	5048	13.3 (11.4, 15.2)	12.5 (10.4, 14.6)
500 mg QD	**6551**	**17.2 (14.7, 19.7)**	**16.1 (13.3, 18.9)**
800 mg QD	8325	21.8 (18.6, 25.0)	20.4 (16.8, 24.0)
1200 mg QD	10,238	26.7 (22.8, 30.7)	25.0 (20.4, 29.5)

[a]For 500 mg QD dosing, the overall geometric mean was calculated from the escalation phase (n=39 patients) and expansion phase (n=134 patients) geometric means as follows: exp(39 / (39 + 134) ln(6710) + 134 / (39 + 134) ln(6505)) = 6551 ng/mL. For other doses C_{max} was approximated, accounting for decreasing bioavailability with dose from the pharmacokinetic model of study AG120-C-001,[8] as follows: 6551 (dose/500)$^{1.046}$

CONCLUSIONS

- These analyses provide a robust assessment of the effect of therapeutic doses of ivosidenib on ΔQTcF in patients with mIDH1 R/R AML.
- At the steady-state geometric mean C_{max} for the recommended clinical dose of 500 mg QD, a ΔQTcF of 16.1 ms (90% CI 13.3, 18.9 ms) was predicted in patients with R/R AML.
  - The upper bound of the 90% CI was <20 ms, which is lower than the limit of health authority concern.[a]
- Guidance on managing the adverse event of QTc prolongation is provided in the prescribing information for ivosidenib.[6]

[a]An upper CI ≥20 ms of the largest mean ΔQTc at any time point after dosing has been suggested as the arbitrary threshold for a large, clinically significant QTc prolongation in the field of oncology.[7]

Acknowledgments

We would like to thank the healthy volunteers and patients taking part in these studies.

Disclosures

This work was funded by Agios Pharmaceuticals, Inc.

KL, BF, HL, ECA, DH, and HY: Agios – employment and stockholder. BP: Certara – employment and stockholder. DD and SVA: Agios – employment and stockholder at the time of the study.

Editorial assistance was provided by Susanne Vidot, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

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Presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting, March 13–16, 2019, Washington, DC, USA