CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211192Orig1s000

OTHER REVIEW(S)

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	211192
Brand Name	TIBSOVO
Generic Name	Ivosidenib (AG-120)
Sponsor	Agios Pharmaceuticals, Inc.
Indication	Treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation
Dosage Form	Tablet
Drug Class	Inhibitor of isocitrate dehydrogenase-1 (IDH1) enzyme
Therapeutic Dosing Regimen	500 mg qd
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Has not established in humans
Submission Number and Date	001 / 12/21/2017
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

Ivosidenib inhibits the hERG potassium channel and is associated with concentration-dependent QTc interval prolongation in clinical studies. The results of a concentration-QTc analysis using data from studies AG120-C-001 and AG120-C-002 are shown by study in Table 1. Daily doses of 500 mg caused mean increases in QTcF from baseline of 18 to 25 ms, respectively. The data from these studies were not pooled because significant variation in the slope estimate was detected. Administration of ivosidenib with high-fat meal or strong or moderate CYP3A4 inhibitors will further increase exposure.

Table 1: The Estimated QTc effect based on concentration-QTc modeling (FDA Analysis)

Study	Treatment	Concentration	Mean ΔQTcF (ms)	90% CI (ms)
AG120-C-001	500 mg qd	6,551 ng/mL	17.3	(15.1, 19.5)
AG120-C-002	500 mg qd	6,551 ng/mL	25.2	(20.8, 29.7)

There were patients with substantial QTc prolongation.

- AG120-C-001:
  - 22 (9%) patients had QTc >500 ms
  - 32 (12%) patients had increase from baseline QTc >60 ms. Please note, that the label notes 14% of patients had an increase from baseline of greater than 60 ms – however in the adeg data set provided in sequence 0008, the reviewer was only able to identify 32 patients (12%).
  - 12 (5%) patients had QTc >500 ms and change from baseline QTc >60 ms.
- AG120-C-002:
  - 2 (1%) patients had QTc > 500 ms
  - 9 (5%) patients had increase from baseline QTc > 60 ms
  - 2 (1%) patients had QTc > 500 ms and change from baseline > 60 ms

In study AG120-C-001, there were 5 patents who experienced cardiac AEs within the MedDRA SMQ Torsade de Pointes/QTc prolongation. Two subjects (b) (6) experienced events of suspected torsade de pointes, however, only one event is thought to be drug-related (b) (6). Three subjects (b) (6) [cardiopulmonary arrest], (b) (6) [ventricular tachycardia], and (b) (6) [syncope]) experienced events which were not likely to be drug-related. See section 5.4 for more details. Cardiac AEs in AG120-C-002 were not evaluated because narratives were not provided.

2 PROPOSED LABEL

We have reviewed the most recent label available (Seq 0028, dated 6/5/2018) and overall we agree with the language in section 2.3, but we have some suggestions for sections 5.2 and 12.2. Our suggestions are marked with highlights below and are suggestions only and we defer final labeling decisions to the Division. Our suggestion of including only 1 of the cardiac AEs is based on Dr. Hicks' cardiology review of the patient narratives.

5.2 QTc Interval Prolongation

Patients treated with TIBSOVO can develop QT (QTc) prolongation [see Clinical Pharmacology (12.2)] and ventricular arrhythmias. Of the 258 patients treated with TIBSOVO in the clinical trial, 9% were found to have a QTc interval greater than 500 msec and 124% of patients had an increase from baseline QTc greater than 60 msec. (b) (4) ne patient developed ventricular fibrillation (b) (4) attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation [see Drug Interactions (7.1), Clinical Pharmacology (12.2)]. Conduct monitoring of electrocardiograms (ECGs) and electrolytes [see Dosage and Administration (2.3)].

In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia [see Dosage and Administration (2.3)].

12.2 Pharmacodynamics

Cardiac Electrophysiology

A concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) was observed at the steady-state C_{max} following a 500-mg daily dose based on an analysis of 171 patients with an IDH1 mutation, including 136 patients with relapsed or refractory AML, who received TIBSOVO 500 mg daily *[see Warnings and Precautions (5.1)]*. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

3 BACKGROUND

3.1 PRODUCT INFORMATION

AG-120 is a selective, potent inhibitor of the isocitrate dehydrogenase-1 (IDH1) mutant protein, being developed for the treatment of patients with cancers that harbor IDH1 mutations, including those with acute myelogenous leukemia (AML). The proposed clinical dosing regimen is 500 mg daily (QD).

3.2 MARKET APPROVAL STATUS

Ivosidenib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In the manual patch clamp assay, AG-120 inhibited IKr (hERG) with an IC20 and IC50 value of 3 and 12.6 μM, respectively. Individual animals with possible (≥30 msec) and probable (≥60 msec) test article-related QTcB prolongation (Morganroth 2001) have been noted in both the 28-day and 3-month GLP cynomolgus monkey studies at free Cmax values ≥0.7-fold the C2D1 500 mg free Cmax human exposure. In addition, prolonged QTcB was observed at the 45 and 135 mg/kg dose levels in a non-GLP single dose monkey CV safety pharmacology study, in which group mean Cmax values were similar to that of individual animals in the 28-day and 3-month repeat-dose studies. Reversibility of the prolonged QTcB effect was assessed in a single high-dose male in the 3-month monkey study; the QTcB levels returned to baseline following the 28-day recovery period (AG120-N-059-R1). Prolonged QTc interval is known to occur at drug concentrations below its hERG IC50 value and can occur at inhibitory concentrations as low as 12-30% (Redfern, et al. 2003). For AG-120, the hERG IC20 is approximately 3 μM, thus hERG inhibition is a plausible explanation for the prolonged QTcB intervals observed in the cynomolgus monkeys.

Reviewer's Comment: Based on the results of the manual patch clamp assay, the hERG safety margin is ~11x, which suggests that the observed QT prolongation in animals, and in the clinical study, could be mediated via direct blockade of the hERG potassium channel.

3.4 PREVIOUS CLINICAL EXPERIENCE

Appendix 6.1 summarizes the previous clinical experience.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ivosidenib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocols for any of the studies included in the proposed concentration-QT analysis, but did provide input on the proposed concentration-QTc approach under IND 119,341 (DARRTS 07/05/2016). The QT-IRT agreed that the proposed concentration-QTc analysis would be adequate to detect large mean changes in the QTc interval, which is acceptable based on the proposed indication.

The proposed concentration-QTc analysis includes three studies: AG120-C-001 (dose escalation/expansion in R/R AML patients, CSR), AG120-C-002 (dose escalation/expansion in patients with solid tumors, CSR) and AG120-C-004 (food effect study in healthy volunteers, CSR). There are differences in dosing and ECG/PK sampling schedule between the two patient studies and the healthy volunteer study and we will therefore focus on our analysis on the two patient studies in our review, except for section 4, which describes the sponsor's pooled concentration-QTc analysis.

The sponsor submitted the "*Concentration-QTc Report AG120-C-META-CQT*" (CSR) for ivosidenib, including electronic datasets and waveforms to the ECG warehouse.

4.2 CONCENTRATION-QT REPORT

4.2.1 Title

Modeling the Relationship Between AG-120 Concentration and Electrocardiogram QTc in Subjects with Advanced Malignancies and Healthy Subjects

4.2.2 Protocol Number

Concentration-QTc Report: AG120-C-META-CQT

4.2.3 Study Dates

Date first subject enrolled:

- AG120-C-001: 12 March 2014
- AG120-C-002: 14 March 2014
- AG120-C-004: 29 September 2015

Date last subject completed:

- AG120-C-001: 12 May 2017 (cutoff for the provided CSR)
- AG120-C-002: Ongoing (cutoff of 12 May 2017 in the interim CSR)
- AG120-C-004: 31 December 2015

4.2.4 Objectives

The objectives of this population concentration-QTc analysis were to:

- Explore and characterize the relationship of change from baseline QTc (ΔQTc) with AG-120 plasma concentration in Study AG120-C-001.
- Explore and characterize the relationship of ΔQTc with AG-120 plasma concentration in pooled data sets of AG120-C-001 together with AG120-C-002 and healthy subjects in AG120-C-004.
- Predict AG-120 concentration-related QTc prolongation with associated confidence intervals at relevant exposures.

4.2.5 Study Description

4.2.5.1 Design

The concentration-QTc report for AG-120 consists three phase 1 studies: AG120-C-001, AG120-C-002, and AG120-C-004. The detail of design for the three studies (001, 002 and 004) that were evaluated in this report are as follows:

AG120-C-001 ("001"): This is an ongoing Phase 1, multicenter, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced hematologic malignancies with an IDH1 mutation, including R/R AML. The study includes a dose escalation portion to determine the maximum tolerated dose and/or the recommended Phase 2 dose and an expansion portion to further evaluate the safety, tolerability, and clinical activity of AG-120 in select populations.

During the dose escalation phase, consented eligible subjects were enrolled into sequential cohorts of increasing doses of AG-120. AG-120 was administered in continuous 28-day cycles at doses of 100 mg twice daily (BID), 300 mg once daily (QD), 500 mg QD, 800 mg QD, and 1,200 mg QD. The first 3 subjects in each cohort received a single dose of AG-120 on Day -3, three days before starting continuous daily dosing, in order to assess the PK/pharmacodynamics profile. On the basis of the available safety, PK/PD, and clinical activity data observed during dose escalation, 500 mg QD was selected as the recommended dose for expansion.

On the basis of the available safety, PK/PD, and clinical activity data observed during dose escalation, 500 mg QD was selected as the recommended dose for expansion. Subjects were enrolled into 1 of 4 arms: (1) R/R AML (n=126 enrolled and received at least 1 dose of study drug), (2) untreated AML (n=25), (3) non-AML IDH1-mutated R/R advanced hematologic malignancies (n=11), and (4) relapsed AML not eligible for Arm 1 (n=18).

Subjects continued treatment with AG-120 until disease progression, development of other unacceptable toxicity, confirmed pregnancy, undergoing a hematopoietic stem cell transplant (HSCT), death, withdrawal of consent, loss to follow-up, or Sponsor ending the study, whichever occurred first.

In the dose escalation portion, time-matched AG-120 concentration and single 12-lead ECG assessments were made on Day -3 (pre-dose and 4 hours post-dose). For all subjects in the dose escalation portion, additional single 12-lead ECG assessments were made on Cycle 1 Day 1, 8, and 15, on Cycle 2 Day 1 and 15, on Day 1 of each treatment cycle thereafter, and at the end of treatment (EOT). The ECG assessment times

were pre-dose (Cycle 1 Day 1 only), four hours post-dose (Cycle 1 only), or anytime (after Cycle 1).

In the expansion portion, time-matched AG-120 concentration and triplicate (approximately 2 minutes apart) 12-lead ECG assessments were made on Day 1 (pre-dose and 3, 4, and 8 hours post- dose) of Cycles 1 and 2, and at EOT. In addition, a single 12-lead ECG was obtained on Cycle 1 Day 8 and 15 (4 hours post-dose). For comparison with these ECG assessment times, the median T_{max} of AG-120 after multiple doses was 2.98 hours [15].

AG120-C-002 ("002"): This is an ongoing multicenter, open-label, dose-escalation study with an expansion portion to evaluate safety/tolerability, MTD, PK/PD relationships, and clinical activity in subjects with advanced solid tumors with an IDH1 mutation. Sampling and design were similar to AG120-C-001.

AG120-C-004 ("004"): This was a two-part study in healthy subjects. Part 1 was an open-label randomized study, with two periods and a crossover design, to determine the effect of food on the PK of a single 500-mg dose. Part 2 was an open-label study to determine safety and PK parameters following a single 1000-mg dose of AG-120. In both parts, time-matched AG-120 concentration and triplicate ECG assessments were made on Day 1. pre-dose, and 1, 2, 4, 24, and 48 hours post-dose. All data with and without food were included in this analysis.

Overall design for the three studies are presented below together with another study that was not included in the pooled analysis (003)

Study Number (patients)	ECG Data Collection	PK Sampling Collection
AG-120-C-001 (R/R AML)	**Dose escalation**: one screening ECG was obtained within 2 weeks of starting therapy to determine eligibility. Serial ECG's were performed at pre-dose and 4 hour on Day -3, Cycle 1 Day 1. On Day 8 and Day 15, single 12-lead ECGs are obtained at 4 hours post-dose. Single 12-lead ECGs are obtained at any time during C2D1, C2D15, C3D1, and Day 1 of each cycle. **Dose expansion**: Time-matched 12-lead ECGs with PK samples will be conducted in triplicate at pre-dose, 3, 4, and 8 hours post-dose on Cycle 1 Day 1 and C2D1. Triplicate ECG also will be conducted at the end of treatment visit. Single 12-lead ECGs will be conducted at Screening, 4 hours post-dose on C1D8, C1D15, C3D1, day 1 of subsequent cycles, and follow-up visit.	**Dose escalation**: Day -3: Pre-dose; 0.5, 1, 2, 3, 4, 6, 8, 10, 24, 48, and 72 hours post-dose. C1D15, C2D1: Pre-dose; 0.5, 1, 2, 3, 4, 6, 8, and 10 hours post-dose. Pre-dose samples on: C1D8, C1D22, C2D15, C3D1, C3D1, Day 1 of subsequent cycles. **Dose expansion**: C1D1 and C2D1: pre-dose, 2, 3, 4, 6, and 8 hours post-dose. Pre-dose samples on: C1D8, C1D15, C3D1, end of treatment visit.
AG-120-C-002 (solid tumors)	**Dose expansion**: time-matched triplicate ECGs will be conducted on Day 1 of Cycles 1 and 2 at the following time points: pre-dose, 3, 4, and 8 hours post-dose. Single 12-lead ECGs will also be conducted on Day 1 of every cycle beginning with Cycle 3.	**Dose expansion**: C1D1 and C2D1 at the following time points: pre-dose, 2, 3, 4, 6, and 8 hours post-dose. Pre-dose on Days 8 and 15 of Cycle 1, C3D1 and end of treatment visit.
AG-120-C-003 (HV)	Triplicate ECGs will be obtained at screening, check-in, on Day 1 at the following time: predose and 1, 2, 4, 24, and 48 hours postdose; and at discharge. The 3 ECGs will be obtained within a 5-minute window at each time point.	Predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 240, 336, 408, and 504 hours post-dose (Day 22).
AG-120-C-004 (HV)	Triplicate ECGs will be obtained at screening, check-in, at Day 1 predose, and at 1, 2, 4, 24, and 48 hours post-dose, and Day 22 EOS.	Day 1 predose, and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 120, 168, 240, 336, and 504 hours post-dose.

Abbreviations: CxDx = cycle x, day x; ECG = electrocardiogram; EOS = end of study; HV = healthy volunteers; PK = pharmacokinetic; R/R AML = relapsed or refractory acute myelogenous leukemia.

Source: DARRTS 01-07-16, Table 12.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

AG120-C-001 ("001"):

- Escalation doses at 100 mg BID, 300 mg QD, 500 mg QD, 800 mg QD and 1200 mg QD
- Expansion dose selected 500 mg QD. Subjects were enrolled into 1 of 4 arms:
  Arm 1: R/R AML (n=126 enrolled and received at least 1 dose of study drug),
  Arm 2: untreated AML (n=25),
  Arm 3: non-AML IDH1-mutated R/R advanced hematologic malignancies (n=11), and
  Arm 4: relapsed AML not eligible for Arm 1 (n=18).

AG120-C-002 ("002"):

- Escalation doses at 100 mg BID, 300 mg QD, 400 mg QD, 500 mg QD, 600 mg QD, 800 mg QD, 900 mg QD and 1200 mg QD
- Expansion dose at 500 mg QD

AG120-C-004 ("004"):

- 500 mg Fasted, 500 mg Fed and 1000 mg Fasted

4.2.6.2 Sponsor's Justification for Doses

The expansion cohorts in AG120-C001 and AG120-C002 evaluated the proposed therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

Ivosidenib was administered without regard to food in both AG120-C001 and AG120-C002 and study AG120-C004 included administration under both fed and fasting conditions.

Reviewer's Comment: An increase in Cmax and AUC of 25% and 98% respectively was observed when ivosidenib is taken with a high-fat meal.

4.2.6.4 ECG and PK Assessments

See above Table.

Reviewer's Comment: Acceptable, the ECG/PK sampling in the two expansion phases is adequate to capture time of peak effect (~3 h) and allow for detection of delayed effects.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

AG120-C-001:
A total of 258 subjects with advanced hematologic malignancies have received at least 1 dose of ivosidenib: 78 subjects were treated in dose escalation (dose range 100 mg BID - 1200 mg QD) and 180 subjects were treated in the expansion phase (500 mg QD).

AG120-C-002:
A total of 168 subjects enrolled and received at least 1 dose of AG-120 across 8 groups at doses of 100 mg BID, 300 mg QD, 400 mg QD, 500 mg QD, 600 mg QD, 800 mg QD, 900 mg QD, and 1,200 mg QD. One-hundred and thirty subjects received 500 mg QD.

AG120-C-004:
A total of 30 subjects entered and 27 completed the study for Part 1. A total of 6 subjects entered and completed the study for Part 2.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

This is a concentration-QTc study.

4.2.7.2.2 Assay Sensitivity

Not applicable.

4.2.7.2.3 Categorical Analysis

Table 2 presented sponsor's categorical analyses for full QT dataset and triplicate dataset from Studies 001 and 002. Table presented counts of records with elevated QTcF (>450, >480, and >500 msec) or ΔQTcF (>30, >60, and >100 msec) by study, visit/time, and dataset.

Table 2: Sponsor's Counts of Elevated Mean QTcF and ΔQTcF Instances by Cycle/Day/Time in Studies AG120-C-001 and AG120-C-002

	Cycle, Day, Hour Post-Dose													
Parameter	D-3 H0	D-3 H4	C1D01 H0	C1D01 H3	C1D01 H4	C1D01 H8	C1D15 H4	C2D01 H0	C2D01 H3	C2D01 H4	C2D01 H8	End of Treat.	Total	No of Subjects
Full QT Dataset, Study AG120-C-001														236
Number of Records	40	38	197	168	173	161	53	150	135	132	131	69	**1447**	—
QTcF > 450 msec	5	10	28	44	46	39	24	39	56	49	41	15	**396**	122
QTcF > 480 msec	0	4	3	6	6	5	3	5	14	10	9	3	**68**	29
QTcF > 500 msec	0	0	1	1	2	1	0	2	3	6	1	0	**17**	10
ΔQTcF > 30 msec	0	5	0	8	10	4	12	26	39	42	32	5	**183**	79
ΔQTcF > 60 msec	0	0	0	0	0	0	0	2	5	3	3	0	**13**	8
ΔQTcF > 100 msec	0	0	0	0	0	0	0	0	1	1	1	0	**3**	2
Full QT Dataset, Study AG120-C-002														164
Number of Records	50	49	125	102	102	101	50	89	95	93	92	46	**994**	—
QTcF > 450 msec	3	6	4	8	9	6	13	7	17	17	13	2	**105**	46
QTcF > 480 msec	0	0	0	0	0	0	0	1	1	1	0	1	**4**	2
QTcF > 500 msec	0	0	0	0	0	0	0	0	0	0	0	0	**0**	0
ΔQTcF > 30 msec	0	4	0	5	4	1	16	8	19	14	11	6	**88**	48
ΔQTcF > 60 msec	0	0	0	0	0	0	2	0	0	1	0	0	**3**	3
ΔQTcF > 100 msec	0	0	0	0	0	0	0	0	0	0	0	0	**0**	0
Triplicate Dataset, Study AG120-C-001														171
Number of Records	—	—	171	166	167	152	—	130	132	127	124	34	**1203**	—
QTcF > 450 msec	—	—	26	42	42	37	—	33	55	48	39	9	**331**	87
QTcF > 480 msec	—	—	2	6	5	5	—	5	14	9	8	2	**56**	22
QTcF > 500 msec	—	—	1	1	1	1	—	2	3	5	0	0	**14**	8
ΔQTcF > 30 msec	—	—	0	8	9	4	—	20	38	41	31	4	**155**	61
ΔQTcF > 60 msec	—	—	0	0	0	0	—	1	5	2	2	0	**10**	6
ΔQTcF > 100 msec	—	—	0	0	0	0	—	0	1	0	0	0	**1**	1
Triplicate Dataset, Study AG120-C-002														107
Number of Records	—	—	107	102	101	100	—	88	93	93	91	19	**794**	—
QTcF > 450 msec	—	—	3	8	9	6	—	7	17	17	12	1	**80**	30
QTcF > 480 msec	—	—	0	0	0	0	—	1	1	1	0	0	**3**	1
QTcF > 500 msec	—	—	0	0	0	0	—	0	0	0	0	0	**0**	0
ΔQTcF > 30 msec	—	—	0	5	4	1	—	8	19	14	11	3	**65**	29
ΔQTcF > 60 msec	—	—	0	0	0	0	—	0	0	1	0	0	**1**	1
ΔQTcF > 100 msec	—	—	0	0	0	0	—	0	0	0	0	0	**0**	0

C: Cycle; D: Day; H: Hour; Treat.: Treatment. Note: Study AG120-C-004 had no QTcF > 450 msec, nor ΔQTcF > 30 msec.

Source: Study Report of ag120-c-meta-cqt.pdf, Table 6-3, page 22.

Reviewer's Comments: We conducted independent categorical analyses based on escalation and expansion cohorts from Studies 001 and 002 at 500 mg QD in Section 5.2 by using "adeg.xpt" dataset.

4.2.7.3 Safety Analysis

The most common adverse reactions (≥20%) of any grade were leukocytosis, diarrhea, nausea, electrocardiogram QT prolonged, and rash.

Serious adverse reactions (≥5%) were IDH differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). No patient had a Grade 4 IDH differentiation syndrome or electrocardiogram QT prolonged event and none of the events of IDH differentiation syndrome, leukocytosis, or electrocardiogram QT prolonged were fatal.

The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), IDH differentiation syndrome (3%), and leukocytosis (3%). Three out of 179 patients (2%) required a dose reduction due to an adverse reaction. The most common adverse reaction leading to a dose reduction was electrocardiogram QT prolonged (1%). No patients permanently discontinued TIBSOVO due to the adverse reaction of electrocardiogram QT prolonged. No patient permanently discontinued or required a dose reduction of TIBSOVO due to IDH differentiation syndrome or leukocytosis adverse reactions. One of 179 patients (0.6%) permanently discontinued TIBSOVO due to rash.

A summary of adverse events by MedDRA preferred term in the broad SMQ for torsade de pointes/QT prolongation is shown below in Table 3.

Table 3: Summary of Grade ≥3 and All-Grade Adverse Events by MedDRA Preferred Term in the SMQ (Broad) Torsade de Pointes/QT Prolongation (Safety analysis set) for study AG120-C-001

	Arm 1+ (N=159)		R/R AML at 500 mg QD (N=179)		Overall (N=258)	
Adverse Event, n (%)	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**
At Least 1 Adverse Event	**17 (10.7)**	**40 (25.2)**	**20 (11.2)**	**46 (25.7)**	**26 (10.1)**	**62 (24.0)**
Electrocardiogram QT prolonged	15 (9.4)	38 (23.9)	18 (10.1)	44 (24.6)	23 (8.9)	58 (22.5)
Syncope	2 (1.3)	2 (1.3)	2 (1.1)	2 (1.1)	2 (0.8)	4 (1.6)
Ventricular tachycardia	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.1)	1 (0.4)	2 (0.8)
Cardiac arrest	0	0	1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)
Cardio-respiratory arrest	0	0	0	0	1 (0.4)	1 (0.4)
Ventricular arrhythmia	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)

Source: CSR AG120-C-001, Table 14.3.1.15.1, Table 14.3.1.15.2, and Table 14.3.1.15.3. Data cutoff date: 12 May 2017.

Source: Summary of clinical safety, Table 21, Page 58

Reviewer's comments: There are two cardiac adverse events that are suspected torsade events as described in section 5.4.1.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results after multiple dosing in study AG120-C-001 is shown below in Table 4.

Table 4: Summary of Ivosidenib Plasma Pharmacokinetic Parameters After Multiple Oral Administration (C2D1) of 500 mg QD Ivosidenib (AG120-C-001)

PK Parameters	Summary Statistic for Dose Expansion by Arm and Overall [1]					Summary Statistic for Escalation and Expansion Combined at 500 mg QD [1]
	Arm 1: R/R AML	Arm 2: Untreated AML	Arm 3: MDS	Arm 4: R/R AML Subjects not Eligible for Arm 1	Overall	
n	92	19	10	13	134	173
$AUC_{0\text{-}8hr}$ (hr•ng/mL)	43,401 (51.0) n=88	43,950 (56.1) n=19	38,773 (48.9) n=10	44,047 (48.5) n=12	43,163 (50.8) n=129	43,486 (47.8) n=168
$AUC_{0\text{-}24hr}$ (hr•ng/mL)	115,916 (52.8) n=91	118,259 (58.0) n=19	102,504 (52.5) n=10	122,229 (52.3) n=12	115,729 (53.0) n=132	117,348 (50.1) n=170
C_{max} (ng/mL)	6,572 (46.2) n=92	6,578 (52.4) n=19	5,716 (49.9) n=10	6,579 (40.6) n=13	6,505 (46.5) n=134	6,551 (44.2) n=173
T_{max}[2] (hr)	2.92 (1.07, 7.92) n=92	3.02 (1.97, 8.02) n=19	3.11 (2.00, 4.00) n=10	3.07 (1.88, 4.15) n=13	3.00 (1.07, 8.02) n=134	3.00 (1.00, 8.02) n=173
CL_{ss}/F (L/hr)	4.31 (52.8) n=91	4.23 (58.0) n=19	4.88 (52.5) n=10	4.09 (52.3) n=12	4.32 (53.0) n=132	4.26 (50.1) n=170
$R_{acc(AUC)}$	1.89 (52.2) n=82	1.80 (54.7) n=19	1.99 (78.9) n=10	1.89 (57.8) n=12	1.88 (54.6) n=123	1.90 (53.9) n=135
$R_{acc(Cmax)}$	1.48 (47.5) n=88	1.38 (50.5) n=19	1.37 (65.7) n=10	1.45 (42.3) n=13	1.45 (48.3) n=130	1.46 (48.1) n=142

Source: CSR AG120-C-001 Table 68 and Report AG120-C-001-PKPD Table 31. Data cutoff date: 12 May 2017.
Abbreviations: AML = acute myeloid leukemia; $AUC_{0\text{-}8hr}$ = area under the concentration × time curve from time 0 to 8 hours postdose; $AUC_{0\text{-}24hr}$ = area under the concentration × time curve from time 0 to 24 hours postdose; CL_{ss}/F = apparent clearance at steady state; C_{max} = maximum concentration; GeoCV = geometric coefficient of variation; MDS = myelodysplastic syndrome; QD = once daily; $R_{acc(AUC)}$ = accumulation ratio (based on AUC), calculated as $AUC_{0\text{-}\tau}$ (C2D1)/$AUC_{0\text{-}12hr}$ or $AUC_{0\text{-}24hr}$ (C1D1); $R_{acc(Cmax)}$ = accumulation ratio (based on C_{max}), calculated as C_{max} (C2D1)/C_{max} (C1D1); T_{max} = time to maximum observed plasma concentration.
[1] Geometric mean (GeoCV%), unless otherwise specified.
[2] Median (minimum, maximum).

Source: Summary of Clinical Pharmacology Studies, Table 14, Page 38

4.2.7.4.2 Exposure-Response Analysis

Consistent with the reviewer's initial assessment, the sponsors assessment showed an absence of a delay between changes in QTcF and ivosidenib concentration and that a linear model would be appropriate to describe the relationship. Afterwards, the sponsor evaluated the model on the full data set and triplicate only dataset as well as by study and the results of the sponsor's assessment is provided below.

Table 6-6 compares slopes in concentration across models for each dataset, combined and by individual study, and for the R/R AML subpopulation of AG120-C-001 (see Table 10-5 through Table 10-12 for parameter estimates). Slopes in the primary final model were similar to those in the corresponding base model. Note that the Study AG120-C-001 slope is sensitive to the single highest outlier (with ΔQTcF = 186.7 msec). The effect of this outlier on Study AG120-C-001 predictions is shown in Table 6-7, discussed below.

Table 5: Comparison of Primary and Supporting Models

Data, Model	No. of Subjects, No. of Records	Conc. Slope (msec/(ng/mL)) 001	002	004	Significant Covariates with Sign (in order of model entry)
Triplicate Combined (**Primary Model**)	314, 2377	0.00258	0.00379	0.00120	Baseline QTcF (-), Age (+), Corrected Calcium 5-day avg. (-), QT-Risk Medications flag (-), Magnesium >mean (-)
Triplicate Combined Base	314, 2377	0.00257	0.00383	0.00127	(Not Applicable)
Triplicate Combined without Highest ΔQTcF	314, 2376	0.00251	0.00372	0.00130	Baseline QTcF (-), Age (+), Corrected Calcium 5-day avg. (-), Potassium (-), QT-Risk Meds flag (-)
Triplicate with No Study Effect	314, 2377	0.00280	0.00280	0.00280	Baseline QTcF (-), Age (+), Corrected Calcium 5-day avg. (-), QT-Risk Medications flag (-), Potassium (-)
Triplicate 001 Only	171, 1203	0.00254	—	—	Baseline QTcF (-), Calcium >mean (+), QT-Risk Medications flag (-), Age (+), Potassium 5-day avg. (-)
Triplicate R/R AML Only	136, 949	0.00240	—	—	Baseline QTcF (-), Calcium >mean (+), Age (+), Potassium 5-day avg. (-)
Triplicate 002 Only	107, 794	—	0.00379	—	Corrected Calcium 5-day avg. (-), Baseline QTcF (-), Glioma flag (-)
Full-Data Combined	436, 2821	0.00242	0.00383	0.00132	Baseline QTcF (-), Age (+), Corrected Calcium 5-day avg. (-), Potassium 5-day avg. (-), QT-Risk Medications flag (-)
Full-Data 001 Only	236, 1447	0.00241	—	—	Baseline QTcF (-), Calcium >mean (+), Potassium 5-day avg. (-), Age (+)
Full-Data 002 Only	164, 994	—	0.00397	—	Corrected Calcium (-), Baseline QTcF (-), Glioma flag (-)

001: AG120-C-001; 002: AG120-C-002; 004: AG120-C-004.
Source: Model Parameter Estimates tables (Table 6-4, Table 6-5, and Table 10-5 through Table 10-12).

Source: Concentration-QTc report, Table 6-6, Page 26

Reviewer's Analysis: The reviewer's independent analysis of the data is shown in section 5.2 and is consistent with the sponsor's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate were observed (see Section 5.3).

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Central Tendency Analysis for Ivosidenib 500 mg QD

All analyses are based on data from Studies 001 and 002. Table 6 presents the summary statistics (mean and standard deviation) and the 90% confidence interval for mean changes of AG-120 at 500 mg daily for Cycles 1 and 2 for the expansion phase. The reason for omitting Cycle 3 or later ECG values was lack of triplicate measurements (see report, Section 4.4.2, page 12).

Using central tendency analysis, for Study 001, the largest upper bound of the 2-side 90% CI on the mean change from baseline in QTcF is 25.3 ms (on Cycle 2 Day 1 at 3-hour post-dose) which is >20 ms. For Study 002, the largest upper bound on the mean change from baseline is 19.8 ms (on Cycle 2 Day 1 at 4-hour post-dose).

Table 6: Analysis Results of ΔQTcF for Ivosidenib 500 mg QD by Study, Cycle, Day and Time (Expansion Cohort)

Study ID	Visit Cycle/Day	Time (H)	N	Mean	Std Dev	90% CI for Mean
AG120-C-001	C1D1	3	174	8.3	13.1	(6.7, 10.0)
		4	177	9.0	13.8	(7.3, 10.8)
		8	168	6.4	12.7	(4.8, 8.0)
	C1D8	4	165	16.6	20.0	(14.0, 19.2)
	C1D15	4	154	13.3	29.0	(9.5, 17.2)
	C2D1	3	137	22.0	23.6	(18.6, 25.3)
		4	137	20.5	22.0	(17.4, 23.6)
		8	136	16.4	24.9	(12.9, 20.0)
AG120-C-002	C1D1	3	107	10.0	10.5	(8.3, 11.7)
		4	107	9.3	11.0	(7.5, 11.1)
		8	107	7.0	11.0	(5.2, 8.7)
	C1D8	4	102	13.8	17.7	(10.9, 16.7)
	C1D15	4	100	14.7	17.4	(11.8, 17.6)
	C2D1	3	97	15.9	16.4	(13.2, 18.7)
		4	96	17.2	15.6	(14.5, 19.8)
		8	95	12.4	15.3	(9.8, 15.0)

Notes: Dataset "qtpk_fda.xpt" is used in the analysis.

5.2.1.2 Sensitivity analysis

Not applicable.

5.2.1.3 Categorical Analysis

lists the number of subjects whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, and >500 ms. Twenty-two subjects from Study 001 and two subjects from Study 002 had QTcF >500 ms.

Table 7: Categorical Analysis of ΔQTcF (Escalation and Expansion Cohort at 500 mg QD)

Study ID	Total N	QTcF<=450 ms	450<QTcF<=480 ms	480<QTcF<=500 ms	QTcF>500 ms
AG120-C-001	258	91 (35.3%)	112 (43.4%)	33 (12.8%)	22 (8.5%)
AG120-C-002	168	95 (56.5%)	68 (40.5%)	3 (1.8%)	2 (1.2%)

Notes: Dataset "adeg.xpt" is used in the analysis.

Table 8 lists the number of subjects' changes from baseline ΔQTc ≤30 ms, between 30 and 60 ms, and >60 ms. Thirty-two subjects from Study 001 and nine subjects from Study 002 had ΔQTcF>60 ms.

Table 8: Categorical Analysis of ΔQTcF (Escalation and Expansion Cohort at 500 mg QD)

Study ID	Total N	Value<=30 ms	30 ms<Value<=60 ms	Value>60 ms
AG120-C-001	258	117 (45.3%)	109 (42.2%)	32 (12.4%)
AG120-C-002	168	92 (54.8%)	67 (39.9%)	9 (5.4%)

Notes: Dataset "adeg.xpt" is used in the analysis.

5.2.2 HR Analysis

The descriptive statistics in ΔHR for central tendency analysis are listed in Table 9. Using central tendency analysis, the largest upper bounds of the 2-sided 90% CI for mean changes from baseline in HR are 4.2 bpm (on Cycle 2 Day 1 at 8-hour post-dose) and 4.5 bpm (on Cycle 1 Day 15 at 4-hour post-dose) from studies 001 and 002, respectively.

Table 9: Analysis Results of ΔHR for Ivosidenib 500 mg QD by Study, Cycle, Day and Time (Expansion Cohort)

Study ID	Visit	Time (H)	N	Mean	Std Dev	90% CI for Mean
AG120-C-001	C1D1	3	178	-0.7	7.3	(-1.6, 0.3)
		4	179	-1.0	7.4	(-1.9, -0.1)
		8	169	-0.1	8.7	(-1.2, 1.0)
	C1D8	4	171	-0.4	10.9	(-1.8, 1.0)

Study ID	Visit	Time (H)	N	Mean	Std Dev	90% CI for Mean
	C1D15	4	159	2.5	12.7	(0.8, 4.1)
	C2D1	3	139	0.7	12.7	(-1.1, 2.5)
		4	141	0.7	11.9	(-0.9, 2.4)
		8	136	2.3	13.4	(0.4, 4.2)
AG120-C-002	C1D1	3	107	0.5	6.4	(-0.6, 1.5)
		4	107	-0.1	6.4	(-1.1, 0.9)
		8	107	0.8	6.4	(-0.2, 1.8)
	C1D8	4	104	2.4	7.9	(1.1, 3.7)
	C1D15	4	100	3.0	9.0	(1.5, 4.5)
	C2D1	3	97	1.7	8.2	(0.3, 3.1)
		4	97	0.9	7.8	(-0.4, 2.2)
		8	96	2.8	8.4	(1.4, 4.2)

Notes: Dataset "qtpk_fda.xpt" is used in the analysis.

5.2.3 PR Analysis

The descriptive statistics in ΔPR for central tendency analysis are listed in Table 10. Using central tendency analysis, the largest upper bounds of the 2-sided 90% CI for mean changes from baselines in PR are 2.0 ms (on Cycle 1 Day 1 at 3-hour post-dose) and 4.0 ms (on Cycle 2 Day 1 at 4-hour post-dose) from studies 001 and 002, respectively.

Table 10: Analysis Results of ΔPR Ivosidenib 500 mg QD by Study, Cycle, Day and Time (Expansion Cohort)

Study ID	Visit	Time (H)	N	Mean	Std Dev	90% CI for Mean
AG120-C-001	C1D1	3	172	0.9	9.0	(-0.2, 2.0)
		4	173	-0.1	9.3	(-1.3, 1.0)
		8	164	0.2	10.0	(-1.1, 1.5)
	C1D8	4	166	-0.5	13.5	(-2.2, 1.2)
	C1D15	4	153	-0.4	14.7	(-2.4, 1.5)
	C2D1	3	135	-1.7	13.7	(-3.7, 0.2)
		4	136	-1.7	14.9	(-3.8, 0.4)
		8	132	-0.8	13.4	(-2.7, 1.2)
AG120-C-002	C1D1	3	107	0.7	8.0	(-0.6, 2.0)
		4	107	0.9	7.6	(-0.3, 2.1)
		8	107	0.2	8.7	(-1.2, 1.5)

Study ID	Visit	Time (H)	N	Mean	Std Dev	90% CI for Mean
	C1D8	4	104	-0.4	11.2	(-2.2, 1.4)
	C1D15	4	100	-1.4	11.0	(-3.2, 0.4)
	C2D1	3	97	0.8	10.0	(-0.9, 2.4)
		4	97	2.3	10.1	(0.6, 4.0)
		8	95	-0.3	10.1	(-2.0, 1.4)

Notes: Dataset "qtpk_fda.xpt" is used in the analysis.
Subjects AG120-C-001 (b) (6), AG120-C-001 (b) (6), AG120-C- (b) (6), and AG120-C-001 (b) (6) have missing PR intervals.

5.2.4 QRS Analysis

The descriptive statistics in ΔQRS for central tendency analysis are listed in Table 11. Using central tendency analysis, the largest upper bounds of the 2-sided 90% CI for mean changes from baselines in QRS are 0.8 ms (on Cycle 2 Day 1 at 3-hour post-dose) and 0.7 ms (on Cycle 1 Day 1 at 3-hour post-dose) from studies 001 and 002, respectively.

Table 11: Analysis Results of ΔQRS for Ivosidenib 500 mg QD by Study, Cycle, Day and Time (Expansion Cohort)

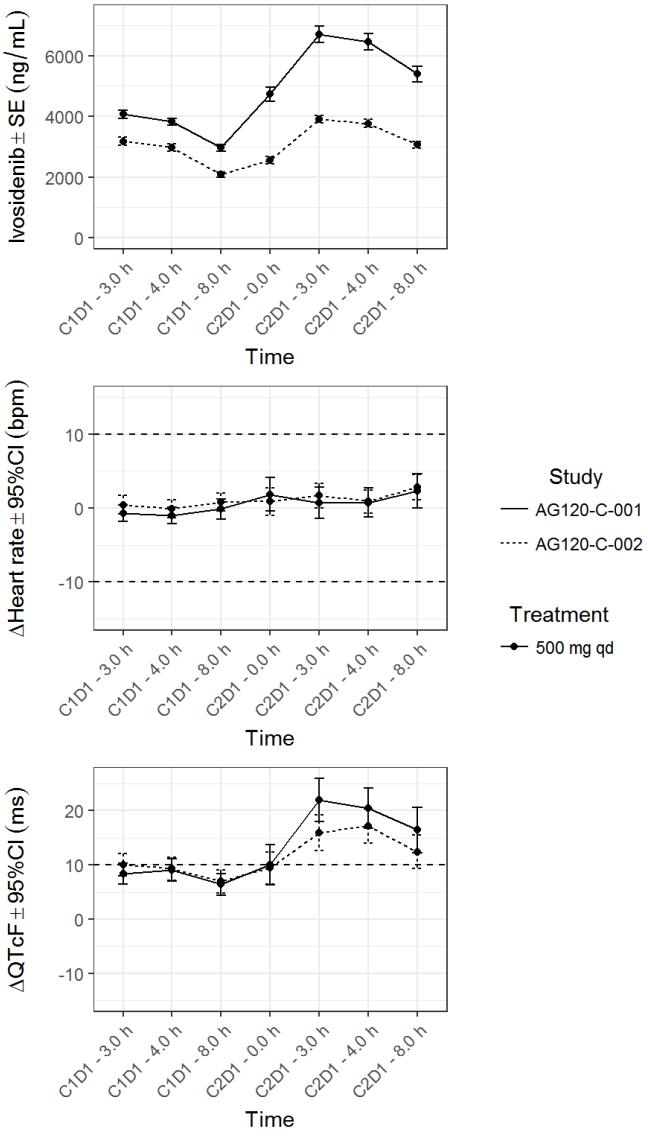
Study ID	Visit	Time(H)	N	Mean	Std Dev	90% CI for Mean
AG120-C-001	C1D1	3	178	0.3	4.0	(-0.2, 0.7)
		4	179	-0.1	4.0	(-0.6, 0.4)
		8	169	-0.1	4.6	(-0.6, 0.5)
	C1D8	4	171	-0.3	6.2	(-1.1, 0.5)
	C1D15	4	159	-0.1	5.9	(-0.9, 0.7)
	C2D1	3	139	-0.1	6.0	(-0.9, 0.8)
		4	140	-0.2	5.9	(-1.0, 0.6)
		8	136	-0.7	5.4	(-1.5, 0.1)
AG120-C-002	C1D1	3	107	0.0	3.8	(-0.6, 0.7)
		4	107	-0.2	3.0	(-0.7, 0.2)
		8	107	-0.6	3.8	(-1.3, -0.0)
	C1D8	4	104	-0.6	4.9	(-1.4, 0.2)
	C1D15	4	100	-0.9	4.7	(-1.7, -0.1)
	C2D1	3	97	-0.1	4.9	(-0.9, 0.7)
		4	97	-0.4	5.0	(-1.3, 0.4)
		8	96	-1.7	5.0	(-2.5, -0.8)

Notes: Dataset "qtpk_fda.xpt" is used in the analysis.

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

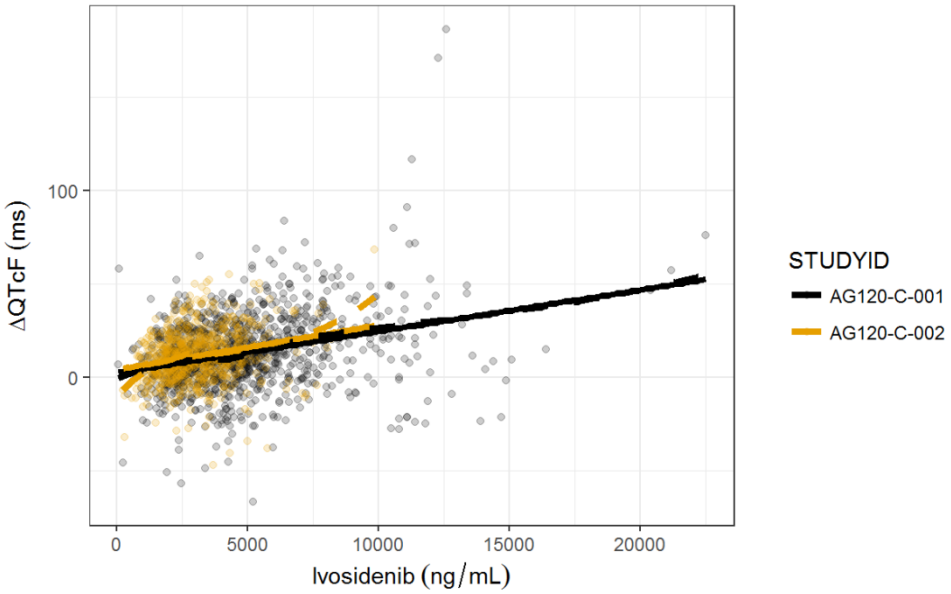
The objective of the clinical pharmacology analysis is to assess the relationship between ivosidenib concentration and ΔQTcF. Of note, the reviewer used a different dataset with the sponsor, however, similar slope and predicted mean effect was observed to that of the sponsor's analysis. Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of ivosidenib pharmacokinetics and changes in ΔHR and ΔQTcF is shown in Figure 1, which shows an absence of significant changes in HR and do not appear to show significant hysteresis.

Figure 1: Time course of ivosidenib concentration (top), heart rate (middle) and QTcF (bottom) for AG120-C-001 (solid) and AG120-C-002 (dashed) for cycle 1 day 1 and cycle 2 day 1 (triplicate ECGs)



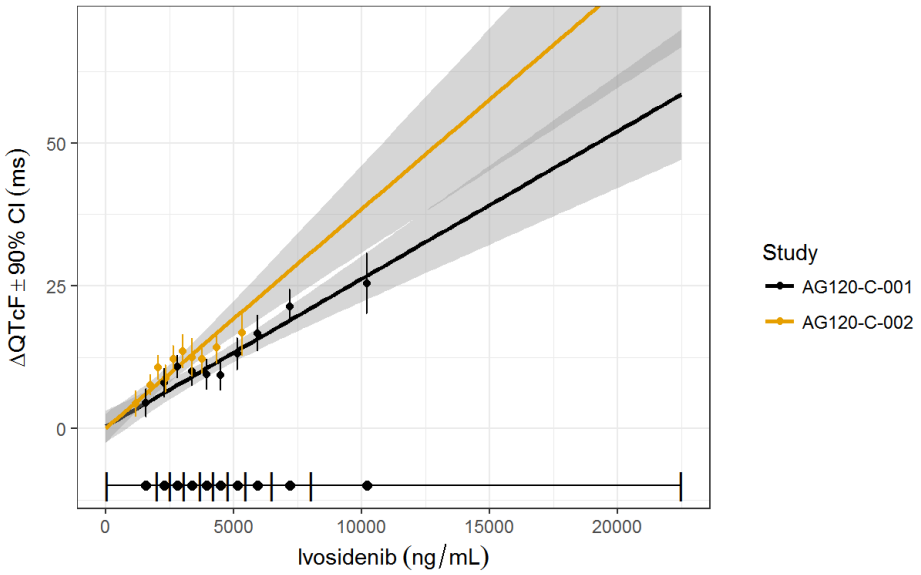
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between ivosidenib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 2 shows the relationship between ivosidenib concentration and ΔQTcF and supports the appropriateness of a linear model by study (AG120-C-001 and AG120-C-002). While, the relationship appears similar between the two studies, a significant difference in the slope of the relationship was observed and it is unknown if this difference is due to a difference in patient population.

Figure 2: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 3, which shows a linear relationship between ivosidenib concentration and ΔQTc by study. A similar conclusion was reached by the sponsor.

Figure 3: Goodness-of-fit plot for QTc



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Table 3 summarizes the adverse events associated with the MeDRA SMQ Torsade/QTc Prolongation in Study AG120-C-001, an open-label, single-arm, multicenter clinical trial in 125 patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH1 mutation who were assigned to receive AG-120 (ivosidenib) 500 mg daily. Dr. Karen Hicks (cardiologist in DCRP) reviewed the narratives for five subjects with cardiac adverse events. In brief, two subjects (b) (6) experienced events of suspected torsade de pointes of which one is thought to be drug-related (b) (6), and three subjects (b) (6) [cardiopulmonary arrest], (b) (6) [ventricular tachycardia], and (b) (6) [syncope]) experienced events which were not likely to be drug-related.

The two events of suspected torsade de pointes for Subjects (b) (6) are described below. In addition to reviewing the narratives, Dr. Hicks reviewed the available ECG waveforms.

1. <u>Subject (b) (6) (syncope and ventricular fibrillation arrest)</u>

Subject (b) (6) is an 83-year-old woman who on Study Day 20 experienced events of syncope and subsequent ventricular fibrillation arrest due to suspected torsade de pointes. The torsade de pointes (TdP) arrhythmia is multifactorial in etiology, and drug effect from ivosidenib cannot be excluded. The supratherapeutic plasma concentration of ivosidenib, electrolyte abnormalities (hypokalemia and hypomagnesemia), and concomitant medications known to cause QT prolongation (fluconazole, amiodarone, and ondansetron) that the subject was receiving in the setting of renal impairment (which further increased the plasma concentration of fluconazole) and heart failure contributed to the events of suspected torsade de pointes.

In brief, Subject (b) (6) received her first dose of ivosidenib 500 mg qd on (b) (6) (Study Day 1) and experienced a syncopal event followed by a ventricular fibrillation arrest on (b) (6) (Study Day 20). Study drug was interrupted on (b) (6) and permanently discontinued on (b) (6) after the subject withdrew consent. On (b) (6) two days after the last dose of study drug, the subject died due to a ventricular arrhythmia. No autopsy was performed.

Subject (b) (6) had received 3 anti-cancer regimens previously but no radiotherapy or bone marrow transplantation for the underlying malignancy. Her past medical history was remarkable for hypokalemia, hypomagnesemia, hypouricemia, and increased alkaline phosphatase. She also had a history of hypotension, uterine brachytherapy, cardiac murmur, mastitis, non-Hodgkin's lymphoma, pleural effusion, pneumonia, radiotherapy, and scarlet fever. Her past surgical history included a colectomy, colostomy, tubal ligation, and tonsillectomy.

Pertinent medical issues at the time of study entry included electrolyte imbalance, hyperglycemia, anemia, epistaxis, nausea, malaise, decreased appetite, asthenia,

hypoalbuminemia, cervical carcinoma, diverticulum, neutropenia, thrombocytopenia, easy bruising, back pain/spinal compression fracture, osteoporosis, and weight loss.

An echocardiogram performed at Screening on (b) (6) demonstrated a left ventricular ejection fraction of 55%.
The Tmax of ivosidenib is approximately 3 hours and the effective $t_{1/2}$ is approximately 24 hours.

There are a number of factors that contributed to the events of syncope (likely due to TdP that spontaneously broke) and subsequent ventricular fibrillation arrest:

1) Concomitant Medications known to prolong the QT Interval, Electrolyte Abnormalities, and Comorbid Conditions

    a. On (b) (6) (Study Day 1), the subject received her first dose of ivosidenib (500 mg orally). According to the narrative, QTcF increased from 430 ms (normal) pre-dose to 452 ms (normal) at 4 hours post-dose. The increase in QTc corresponded to the Tmax of the drug product. On Study Day 1, the subject was also receiving fluconazole, levofloxacin, and ondansetron which could also have contributed to the increase in QTc. Although potassium and magnesium were within normal limits at baseline, both were "low normal" values. The potassium value was 3.9 mmol/L (normal range: 3.5 – 5 mmol/L) and magnesium value was 0.782 mmol/L (normal range: 0.741 – 1.193 mmol/L). Calcium was normal at 2.4 mmol/L (normal range: 2.1 – 2.55 mmol/L). On Study Day 1, the subject was not receiving any electrolyte therapy.

    b. On (b) (6) (Study Day 12), the subject experienced a urinary tract infection (UTI). According to the narrative, the subject was receiving levofloxacin on Study Day 1, but levofloxacin was discontinued on Study Day 12. It is unclear which antibiotic was prescribed for the treatment of the UTI. Although levofloxacin can prolong the QT interval, this medication probably did not contribute to the subsequent events of syncope and ventricular fibrillation arrest on (b) (6).

    c. On (b) (6) (Study Day 20), the subject experienced a syncopal event and reported to the Emergency Room. She was hypokalemic (potassium value of 2.7 mEq/L (normal range: 3.5 – 5.0 mEq/L) and hypomagnesemic (magnesium value of 1.6 mg/dL (normal range of 1.8-2.9 mg/dL). She was admitted to the Intensive Care Unit but experienced a ventricular fibrillation arrest later that same day from which she was successfully resuscitated. She was intubated and started on intravenous (IV) amiodarone while still receiving fluconazole and ondansetron. Therapy with potassium chloride and magnesium sulfate was also initiated.

    Fluconazole, ondansetron, and amiodarone can prolong the QT interval. QT prolonging medications and electrolyte abnormalities can contribute to events of TdP.

The subject's clinical status had deteriorated significantly. On (b) (6), she was in heart failure with a brain natriuretic peptide level of 1885 pg/mL (normal range: 0-100 pg/mL) and had renal impairment (serum creatinine of 1.91 mg/dL [normal range: 0.6 – 1.0 mg/dL]. She was also neutropenic (absolute neutrophil count [ANC] of 0.32 x 10^3/µL, leukopenic (white blood cell count of 0.5 x 10^9/L [normal range: 4.0 – 11.0 x 10^9/L), anemic (hemoglobin of 7.6 g/dL (normal range: 12.0 – 16.0 g/dL), and thrombocytopenic (platelet count of 24 x 10^3/µL [normal range: 140-440 x 10^3µL]. Following the arrest, no cardiac consultation was obtained and no repeat echocardiogram was performed. According to the narrative, no recent cardiac ischemia had been reported and blood cultures were "negative for growth." Following the arrest, the medical team met with the family to discuss the subject's worsening clinical status, and the family elected to transition the subject to hospice care. With the exception of IV fentanyl and versed for sedation, all additional support was withdrawn (i.e., the subject was removed from the ventilator and all antibiotics, vasopressors, laboratory draws, and radiology investigations were discontinued).

Study treatment was interrupted on (b) (6) (Study Day 20) and was discontinued permanently on (b) (6) when the subject withdrew consent. On (b) (6) (two days after the last dose of ivosidenib), the subject died due to ventricular arrhythmia. The family did not request an autopsy.

2) High ivosidenib concentrations

Plasma concentrations of ivosidenib in this subject ranged between 13,000 to 17,000 ng/ml compared to a geometric mean C_{max} of approximately 6,551 ng/ml in healthy volunteers. These high concentrations could be caused by drug interaction with fluconazole (CYP 3A4 inhibitor) and renal impairment (~10% renally eliminated). At the time of the events of syncope and ventricular fibrillation arrest on (b) (6) (Study Day 20), the plasma concentration of fluconazole was also likely markedly elevated because of renal impairment. In addition, the subject was receiving ondansetron and amiodarone, two drug products known to prolong the QT interval. In patients with severe renal impairment, the mean plasma clearance of ondansetron can be reduced by approximately 50%.

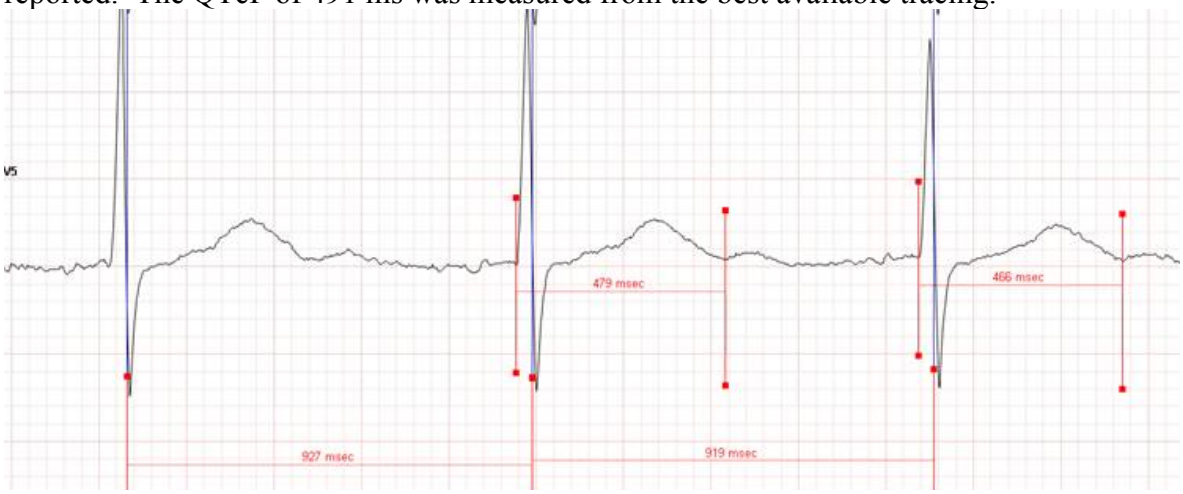
Following the events of syncope and ventricular fibrillation arrest, treatment with ivosidenib was interrupted on (b) (6) and permanently discontinued on (b) (6).

On (b) (6) (two days after the last dose of ivosidenib), the subject reportedly died due to "ventricular arrhythmia." Given the effective $t_{1/2}$ of 24 hours, which could be altered in the setting of drug-drug interactions and renal impairment, it is expected that the plasma concentration of ivosidenib was still elevated at that time as was the plasma concentration of fluconazole.

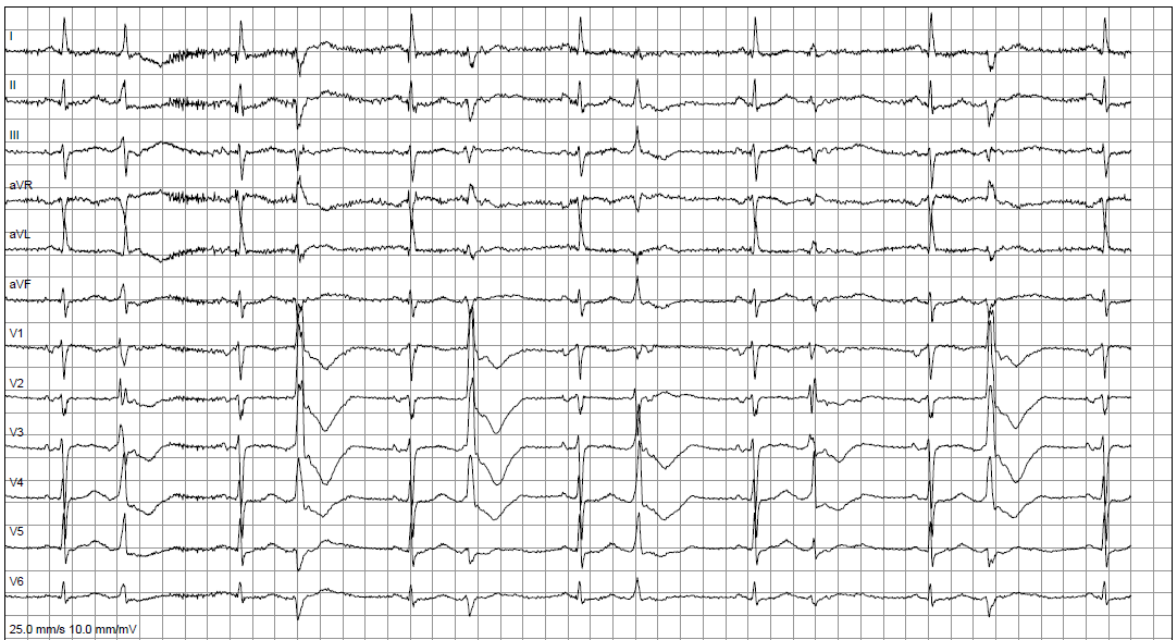
Although the subject had a number of risk factors for QTc prolongation and TdP, the sponsor did not report QTc prolongation. Dr. Hicks reviewed the ECG waveforms as follows:

- QTcF values for Day 1 ([redacted] (b) (6)) at 4 hours post-dose were 448 and 455 ms, similar to what the sponsor reported (QTcF 452 ms).

- QTcF values for Day 8 ([redacted] (b) (6)) at 4 hours post-dose ranged between 479 and 491 ms (prolonged), compared to a QTcF of 447 ms which the sponsor reported. The QTcF of 491 ms was measured from the best available tracing.



- QTcF values for Day 15 ([redacted] (b) (6)) at 4 hours post-dose could not be measured because of the frequent premature ventricular contractions (PVCs) and because no QT interval could be identified clearly.



- No tracings were available from (b) (6) (Study Day 20) when the subject experienced the events of syncope and ventricular fibrillation arrest and from (b) (6) (Study Day 22) when the subject died due to a ventricular arrhythmia.

2. Subject (b) (6) (QT prolongation and cardiac arrest)

Subject (b) (6) was a 60-year-old woman who was hospitalized for febrile neutropenia on (b) (6) and for osteomyelitis on (b) (6). She also experienced nonserious right breast mastitis on (b) (6), QT prolongation on (b) (6), acute kidney injury, hyperkalemia, and mental status changes on (b) (6) cardiac arrest on (b) (6) (11 days after the final dose of study treatment), and death on (b) (6) (24 days after the final dose of study treatment).

In brief, the event of QT prolongation on (b) (6) (Study Day 113) was likely related to ivosidenib and fluconazole. That the QT prolongation resolved with the permanent discontinuation of fluconazole suggests that the primary culprit was fluconazole because a follow-up ECG four days after resuming ivosidenib reportedly demonstrated a normal QTc. The event of cardiac arrest on (b) (6) (11 days after the final dose of study treatment) was not related to ivosidenib. The cardiac arrest was likely due to the subject's worsening clinical status to include renal impairment, thrombocytopenia, anemia, ± hyperkalemia. The subject also received ondansetron one day prior to the cardiac arrest which could also have caused QT prolongation. Ondansetron has a $t_{1/2}$ of approximately 4.0 hours, and mean plasma clearance is reduced by about 50% in patients with severe renal impairment (i.e., creatinine clearance < 30 mL/min).

This subject had received 1 prior anti-cancer regimen for the underlying malignancy which included intensive and investigational therapies but no radiotherapy or bone marrow transplant.

Her past medical history included gastrointestinal hemorrhage, anemia, thrombocytopenia, diarrhea, febrile neutropenia, neutropenic colitis, abdominal distension, and skin neoplasm excision. Her past surgical history was remarkable for cholecystectomy, tubal ligation, and tonsillectomy.

Pertinent medical issues at the time of study entry included hypertension, asthma, gastroesophageal reflux disease, urinary incontinence, vitamin B12 deficiency, easy bruising, and anxiety.

An echocardiogram at Screening showed a normal left ventricular ejection fraction of 63% on (b) (6)

I summarize Subject (b) (6)'s clinical course as follows:

1) According to the narrative, Subject (b) (6) received her first dose of ivosidenib on (b) (6) (Study Day 1). The average pre-dose QTcF interval measured

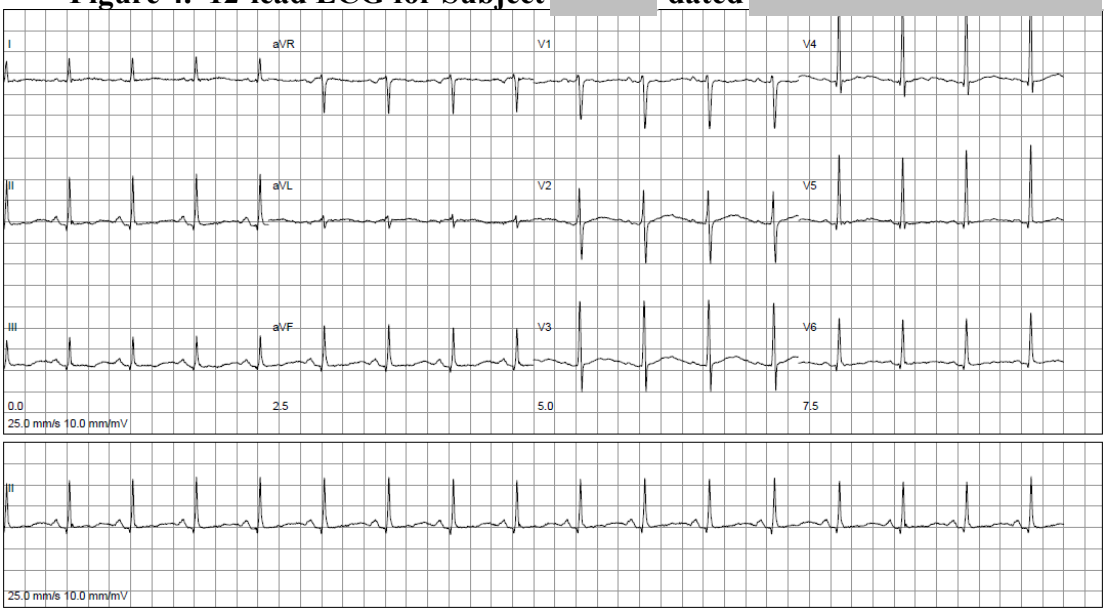
416 ms and 4 hours post-dose QTcF interval measured 428 ms. Laboratory tests demonstrated a calcium level of 2.425 mmol/L (normal range: 2.05-2.55 mmol/L), potassium level of 3.9 mmol/L (normal range: 3.6-5 mmol/L), and a magnesium level of 0.864 mmol/L (normal range: 0.658-1.07 mmol/L). Hence, calcium level was normal and potassium and magnesium levels were "low normal." The subject was also neutropenic (neutrophil count 0.31 x 10^9/L [normal range: 1.5-7.4 x 10^9/L) and leukopenic [white blood cell count 0.88 x 10/L (normal range: 4-11 x 10^9/L). On Study Day 1, the subject was on levofloxacin and was afebrile.

2) On (b) (6) (Study Day 32), the subject was hospitalized for the serious adverse event (SAE) of "febrile neutropenia" with a fever of 100.2 degrees Fahrenheit. She also complained of diarrhea, nausea, and vomiting which she attributed to recent chemotherapy. The subject was initiated on vancomycin and aztreonam. Concomitant medications included acyclovir, cefpodoxime proxetil, famotidine, levofloxacin, paracetamol, prochloperazine, sucralfate, tramadol, and zolpidem. All blood and urine cultures were negative. Clostridium difficile testing results were negative. On (b) (6) (Study Day 34), metronidazole was added to the antibiotic regimen, and she became afebrile. On (b) (6), she was leukopenic (white blood cell count was 2.13 x 10^9/L) and anemic (hemoglobin value was 7.0 g/dL [normal range: 12.0-15.0 g/dL). She was discharged from the hospital on (b) (6) (Study Day 35) when the event of febrile neutropenia was "resolved."

3) On (b) (6) (Study Day 79), the subject was hospitalized for the SAE of osteomyelitis, confirmed by MRI of the right shoulder and right sternoclavicular joint. She was started on IV vancomycin and cefepime. On (b) (6), the subject was diagnosed with a nonserious right breast mastitis, identified by ultrasound. Metronidazole was added to her antibiotic regimen. On (b) (6) (Study Day 88), the narrative indicates that "the osteomyelitis was resolved and the subject was discharged from the hospital on a 6-week course of antibiotics" (i.e., vancomycin and cefepime).

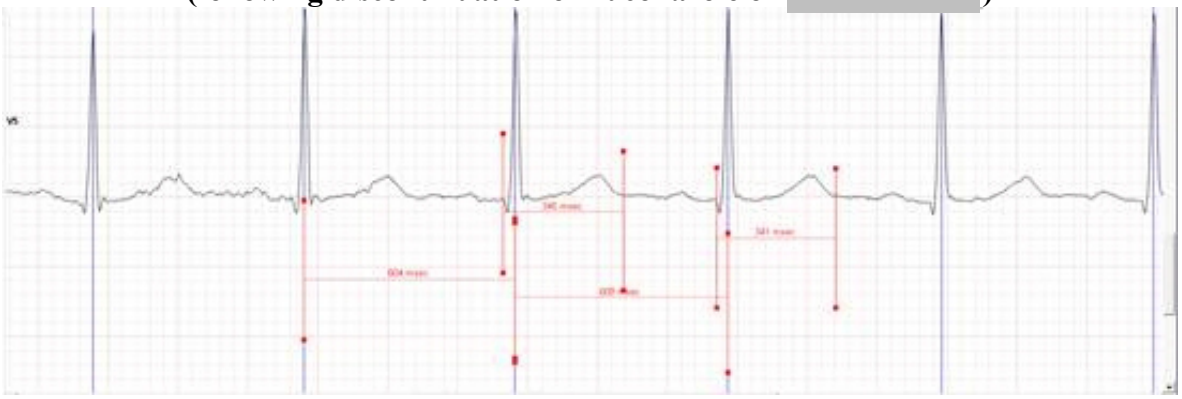
4) On (b) (6) (Study Day 113), the subject's clinic ECG at (b) (6) demonstrated marked QT prolongation as shown in Figure 4. The subject was on fluconazole at the time and calcium, potassium, and magnesium values were reportedly normal. Renal function values were not reported. On (b) (6), ivosidenib and fluconazole were discontinued while treatment with potassium was ongoing. Metronidazole was continued until (b) (6) (Study Day 120). Although prescribing information for metronidazole indicates that "flattening of the T-wave may be seen in electrocardiographic tracings," because subsequent ECGs demonstrated resolution of the findings suggests that metronidazole was non-contributory to the QT prolongation.

Figure 4. 12-lead ECG for Subject [redacted] dated [redacted]



5) On [redacted] (Study Day 114), ECG changes were resolving as shown in Figure 5 and ivosidenib was resumed at the previous dose (500 mg qd). On [redacted] (Study Day 118), the event of "electrocardiogram QT prolonged" was reportedly resolved, suggesting that the primary culprit was fluconazole.

Figure 5. 12-lead ECG for Subject [redacted] dated [redacted] (following discontinuation of fluconazole on [redacted])



6) On [redacted] (Study Day 124), the subject began experiencing mental status changes. She received her final dose of ivosidenib on [redacted] (Study Day 124).

7) On [redacted] (one day after the final dose of ivosidenib), the subject was hospitalized for the SAEs of acute kidney injury and a 2-day history of mental status changes. She also experienced hematemesis, thrombocytopenia, and hyperkalemia (potassium 6.0 [units and normal range not provided]. Given that her vancomycin level was elevated at 106.2, IV vancomycin which had been

administered as an outpatient for treatment of osteomyelitis since (b) (6), was discontinued. CT scan of the head, Chest X-ray, and an ECG were reportedly unremarkable. The subject was guaiac positive by hemoccult testing. At this time, the subject had significant renal impairment and was anemic (hematocrit of 19.5) and thrombocytopenic (platelet count 13,000). Potassium was 5.8. All blood, urine, and clostridium difficile cultures were negative. On (b) (6), a fecal occult blood test was positive, and the subject was transfused one unit of packed red blood cells and 1 unit of platelets. On (b) (6), a colonoscopy demonstrated ulcers consistent with cytomegalovirus colitis.

8) On (b) (6), 11 days following the final dose of ivosidenib, the subject experienced a cardiac arrest and was found to be unresponsive. Cardiopulmonary resuscitation was initiated, and the first rhythm check reportedly demonstrated ventricular fibrillation with possible TdP. The subject was successfully resuscitated with 3 shocks at 225 joules, chest compressions, magnesium, and epinephrine. The subject had received one dose of ondansetron the day prior to the arrest but otherwise was not receiving any medications known to prolong the QT interval. The subject was transferred to the ICU, but Cardiology found no evidence of active ischemia and given the recent thrombocytopenia and guaiac positive stool, deferred cardiac catheterization. Although the neurologist thought he witnessed a full complex nonserious seizure, this event was actually the cardiac arrest. Head CT scan was negative for acute intracranial abnormality. The subject was placed on a cooling protocol, and the event of cardiac arrest was resolved the same day. A warming protocol was initiated on (b) (6) and a repeat ECG showed normal sinus rhythm at 77 bpm. On (b) (6), the subject was awake, alert, and neurologically intact, at which time she was extubated.

9) On (b) (6) (24 days after the last dose of study treatment), the subject died due to progression of disease. The events of acute kidney injury and mental status changes were ongoing at the time of death.

Hence, the QT prolongation on (b) (6) may have been related to the combination of fluconazole and ivosidenib, but primarily fluconazole. The cardiac arrest was unrelated to ivosidenib.

5.4.2 ECG Assessments

Overall ECG acquisition and interpretation in both studies appears acceptable. However, in study AG120-C-001, 7.9% of the QT measurements were associated with QT bias greater than the ECG warehouse thresholds. Therefore, a more comprehensive assessment of QT bias was conducted. The analysis was conducted by study and either overall or by ECG type (single vs. triplicate) as the triplicate ECGs were used for the primary analysis. No significant negative QT bias was observed in this analysis and the detailed results by study are included below. However, it should be noted that the QT bias slope analysis was developed for assessment of QT bias in the absence of QT prolongation and T-wave morphology alteration. The meaning of lack of negative bias and difference in QT bias per ECG warehouse statistics is therefore unknown.

5.4.2.1 AG120-C-001

While 7.9% of the ECGs met the criteria for significant QT bias by the ECG warehouse criteria, no significant negative QT bias was observed (Table 12 and Table 13).

Table 12: QT bias assessment for AG120-C-001

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	5389	5.54 (16.34) ms	-1.97 [-2.65 to -1.29] ms per 100 ms
Single ECG data	2168	5.41 (16.76) ms	-2.25 [-3.32 to -1.18] ms per 100 ms
Triplicate ECG data	3221	5.62 (16.05) ms	-1.75 [-2.64 to -0.87] ms per 100 ms

Table 13: QTcF bias assessment for AG120-C-001

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	5389	5.97 (17.99) ms	-6.5 [-7.64 to -5.36] ms per 100 ms
Single ECG data	2168	5.84 (18.52) ms	-6.95 [-8.81 to -5.09] ms per 100 ms
Triplicate ECG data	3221	6.06 (17.64) ms	-6.21 [-7.65 to -4.77] ms per 100 ms

5.4.2.2 AG120-C-002

No significant negative QT bias was observed and 3% of the ECGs met the criteria for significant QT bias as defined by the ECG warehouse criteria (Table 14 and Table 15).

Table 14: QT bias assessment for AG120-C-002

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	3811	6.78 (9.91) ms	-0.52 [-1.31 to 0.27] ms per 100 ms
Single ECG data	1703	6.82 (9.86) ms	-0.15 [-1.43 to 1.12] ms per 100 ms
Triplicate ECG data	2108	6.75 (9.96) ms	-0.8 [-1.81 to 0.22] ms per 100 ms

Table 15: QTcF bias assessment for AG120-C-002

Treatment	# of ECGs	mean (sd)	Slope [95% CI]
ALL	3811	7.14 (10.79) ms	-4.7 [-5.92 to -3.48] ms per 100 ms
Single ECG data	1703	7.14 (10.49) ms	-4.21 [-6.15 to -2.27] ms per 100 ms
Triplicate ECG data	2108	7.13 (11.02) ms	-5 [-6.56 to -3.43] ms per 100 ms

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

From IND 119341, Seq 0094

Therapeutic dose	The proposed clinical dosing regimen is 500 mg daily (QD). The associated PK parameters for the 500 mg QD dosing regimen are as follows: • After a single dose of 500 mg on Day -3, AUC_{0-72} =148000 (56600) hr*ng/mL, C_{max}=4800 (2040) ng/mL • At steady state at 500 mg QD (Cycle 2 Day 1), AUC_{0-10} = 57200 (21600) hr*ng/mL, C_{max}= 7040 (2490) ng/mL	
Maximum tolerated dose	Maximum tolerated dose has not been established in humans. Preliminary Phase 1/2 clinical safety data have shown that AG-120 is generally well tolerated at 1200 mg QD. Based on the PK/PD, safety and efficacy data, a dose regimen of 500 mg QD has been selected as the proposed clinical dose.	
Principal adverse events	As of 16 January 2016, safety data are available for 119 patients in Study AG120-C-001 (a phase 1 study in patients with advanced AML and related hematologic malignancies that harbor an IDH1 mutation, and 122 patients in Study AG120-C-002 (a phase 1 study in patients with advanced solid tumors, including glioma, with an IDH1 mutation) who have been administered AG-120 on both BID and QD dosing regimens at total daily doses ranging from 200 to 1200 mg. Two dose-limiting toxicities (DLTs) have been reported in Study AG120-C-001. One patient, who was receiving 800 mg QD, experienced Grade 3 QTc prolongation without associated cardiac symptoms; QTc returned to normal following a 3-day drug hold. The patient, who had achieved complete remission (CR), remained on treatment at a reduced dose of 500 mg QD with Grade 1 QTc prolongation until discontinuing treatment to receive a bone marrow transplant. Another patient, receiving 1200 mg QD, experienced a Grade 3 maculopapular rash on the face, trunk, and extremities with paresthesia that resolved to Grade 0-1 following a 5-day drug hold. The dose was subsequently reduced to 800 mg QD, and as of 16 January 2016, the patient remains on study in CR. There have been no DLTs reported in Study AG120-C-002. The most commonly reported treatment-emergent adverse events (TEAEs) across both patient studies (N=241) were nausea (22%), fatigue (22%), diarrhea (19%), anemia (13%), peripheral edema (13%), prolonged QT interval (13%), and vomiting (12%). The most commonly reported SAEs as of the data cutoff date were febrile neutropenia (18%), pneumonia (8%), pyrexia (8%), leukocytosis (6%), and sepsis (5%).	
Maximum dose tested	Single Dose	In patients: 1200 mg In healthy subjects: 1000 mg
	Multiple Dose	In patients: 1200 mg QD
Exposures Achieved at Maximum Tested Dose	Single Dose (Mean and SD)	C_{max}: 6800 (1650) ng/mL AUC_{0-10}: 48400 (15300) hr*ng/mL (Study AG120-C-001)
	Multiple Dose (Mean and SD)	C_{max}: 11400 (1840) ng/mL AUC_{0-10}: 97400 (13900) hr*ng/mL (Study AG120-C-001)

Range of linear PK	Following single-dose (100 to 1200 mg) administrations of AG-120, the $AUC_{0-\infty}$ and C_{max} of AG-120 increased less than proportionally. After multiple dose, exposure increase less than dose proportional between 300 mg QD and 1200 mg QD.	
Accumulation at steady state	Approximately 2.3-fold for QD regimen.	
Metabolites	No major circulating metabolites in AML patients and healthy subjects.	
Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of AG-120 in humans has not been determined because AG-120 has low solubility and no intravenous formulation was available.
	T_{max}	3.0 hr (1.0-6.0) for parent drug
Distribution	Vd/F	Population PK: Vc/F (Vd/F of the central compartment): 27.7 L (78.9% CV) Vp/F(Vd/F of the peripheral compartment): 143 L (73.3% CV)
	% bound	Concentration dependent: 95.6% from 0.2 to 1 μM and 91.6% at 10 μM
Elimination	Route	Primary route: fecal elimination. Human AME study (a single oral dose of 500 mg ^{14}C-AG-120 suspension): • 77.4% of total radioactivity was excreted in feces (with 67% of total radioactivity as unchanged AG-120). • 16.9% of total radioactivity was excreted in urine (with 10% as unchanged AG-120). • Unchanged AG-120 represented the majority of the circulating total radioactivity in plasma.
	Terminal $t_{½}$	Single 500 mg dose in healthy subject: 55 hours Single dose in patients: 75 hours
	CL/F_{ss}	Population PK steady-state CL/F: 2.2 L/hr (CV: 46.3%)
Intrinsic Factors	Age	Not significant in population PK covariate analysis (with limited age range)
	Sex	Not significant in population PK covariate analysis
	Race	Not significant in population PK covariate analysis
	Hepatic & Renal Impairment	Not significant in population PK covariate analysis (with limited range of creatinine clearance, AST/ALT)
Extrinsic Factors	Drug interactions	Planned DDI with a strong CYP3A inhibitor (itraconazole)
	Food Effects	Study conduct completed and analysis is ongoing.

Expected High Clinical Exposure Scenario	The exposure associated with multiple dose of 1200 mg at steady-state was considered to be the expected supra-therapeutic exposure (mean and SD): C_{max}: 11400 (1840) ng/mL AUC_{0-10}: 97400 (13900) hr*ng/mL
Preclinical Cardiac Safety	Multiple safety pharmacology studies, both *in vitro* and *in vivo*, have been conducted to address the potential CV effects of AG-120 including automated (AG120-N-005-R1 and AG120-N-009-R1) and manual (AG120-N-054-R1) patch clamp assays for potential inhibition against currents known to be associated with prolonged QTc, a non-GLP single-dose CV safety pharmacology study in cynomolgus monkeys (AG120-N-064-R1), and ECG assessments included in the 28-day and 3-month GLP cynomolgus monkey studies (AG120-N-001-R1 and AG120-N-059-R1). In the manual patch clamp assay, AG-120 inhibited IKr (hERG) with an IC_{20} and IC_{50} value of 3 and 12.6 μM, respectively. Individual animals with possible (≥30 msec) and probable (≥60 msec) test article-related QTcB prolongation (Morganroth 2001) have been noted in both the 28-day and 3-month GLP cynomolgus monkey studies at free C_{max} values ≥0.7-fold the C2D1 500 mg free C_{max} human exposure (500 mg is the dose selected for the expansion phase of the ongoing Phase 1 clinical trial, Study AG120-C-001). In addition, prolonged QTcB was observed at the 45 and 135 mg/kg dose levels in a non-GLP single dose monkey CV safety pharmacology study, in which group mean C_{max} values were similar to that of individual animals in the 28-day and 3-month repeat-dose studies. Reversibility of the prolonged QTcB effect was assessed in a single high-dose male in the 3-month monkey study; the QTcB levels returned to baseline following the 28-day recovery period (AG120-N-059-R1). Prolonged QTc interval is known to occur at drug concentrations below its hERG IC_{50} value and can occur at inhibitory concentrations as low as 12-30% (Redfern, et al. 2003). For AG-120, the hERG IC_{20} is approximately 3 μM, thus hERG inhibition is a plausible explanation for the prolonged QTcB intervals observed in the cynomolgus monkeys. Electrocardiogram assessments in the 28-day GLP monkey study identified test article-related ventricular bigeminy in one high dose male and female animal (270 mg/kg/day); there was no histopathologic or electrolytic correlate. Reversibility was not assessed. It is unlikely that the observed ventricular bigeminy is due to hERG inhibition, and the cause of this finding remains unclear. The Day 27 free C_{max} values in the 2 animals with ventricular bigeminy were ≥5-fold the C2D1 500 mg free C_{max} human exposure level (AG120-C-001). Ventricular bigeminy was not observed in the dedicated single-dose CV study or in the 3-month GLP monkey study, despite similar exposures having been achieved.

Clinical Cardiac Safety

As of 16 January 2016, safety data are available for 119 patients in Study AG120-C-001, and 122 patients in Study AG120-C-002 who have been administered AG-120 on both BID and QD dosing regimens at total daily doses ranging from 200 to 1200 mg.

Total Number of Patients Treated by Dose Group in Study AG120-C-001 (16 Jan 2016 data cut)

	Escalation					Expansion	
Dose Group	**100 mg BID**	**300 mg QD**	**500 mg QD**	**800 mg QD**	**1200 mg QD**	**500 mg QD**	**Overall n (%)**
Total Number of Patients Treated	4	4	48	15	7	41	119

Total Number of Patients Treated by Dose Group in Study AG120-C-002 (16 Jan 2016 data cut)

Dose Group	**100 mg BID**	**300 mg QD**	**400 mg QD**	**500 mg QD**	**600 mg QD**	**800 mg QD**	**900 mg QD**	**1200 mg QD**	**Overall n (%)**
Total Number of Patients Treated	4	9	5	84	5	6	4	5	122

As of 16 January 2016, five patients in Study AG120-C-001 experienced Grade 3 QTc prolongation AEs; one event was reported as a DLT. Two patients in Study AG120-C-002 experienced Grade 3 QTc prolongation. An overview of QT prolongation AEs in AG120-C-001 and AG120-C-002 studies is shown below.

QTc Prolongation in Study AG120-C-001 and AG120-C-002 (16 Jan 2016 data cut)

	Grade ≥ 3	**All**
Study AG120-C-001 Overall (N=119)		
Electrocardiogram QT Prolonged	5 (4.2)	19 (16.0)
Study AG120-C-002 (N=122)		
Electrocardiogram QT Prolonged	2 (1.6)	12 (9.8)

An additional review of relevant serious adverse events from the ongoing clinical studies was performed in May 2016 for adverse events that may signal potential proarrhythmic effects, as defined in the ICH E14 (i.e. torsade de pointes; sudden death; ventricular tachycardia; ventricular fibrillation and flutter; syncope; seizures).

A total of 4 patients enrolled in Study AG120-C-001 experienced the adverse events of interest. Summary narratives of each event are provided below. None of the events were considered related to study drug administration by the Investigator.

- Subject (b) (6) experienced an event of cardiac arrest 18 days after starting AG-120 at 800 mg per day. The patient presented initially with hypoxia, tachycardia and leukocytosis and died later in intensive care. The autopsy

	results showed multiple pulmonary thromboemboli in the few sections of lung examined suggesting that there was diffuse clotting in the lungs and was the cause for his peri-mortem tachycardia and hypoxia. The cause of death was considered to be AML. • Subject (b) (6) had reported ventricular arrhythmias (ventricular tachycardia and fibrillation) 19 days after starting AG-120 at 500 mg per day. Initially, she was treated for culture positive urinary tract infection. A few days later, she presented to ER with a syncopal episode and found to have hypokalemia and hypomagnesemia. ECG reviewed by the Sponsor showed QT > 500 milliseconds with premature ventricular contractions. She experienced two episodes of ventricular tachycardia in ER and she was transferred to ICU where she was resuscitated for ventricular fibrillation and was given amiodarone. Following the arrest, supportive care was withdrawn and the patient was transferred to hospice care and subsequently died. • Subject (b) (6) received AG-120 for 122 days at 500 mg per day. During AG-120 treatment, ECGs reviewed by the Sponsor were normal and QTcF was less than 450 msec. She experienced a ventricular fibrillation arrest twelve days after stopping AG-120 after she developed acute kidney injury due to elevated vancomycin levels. An ECG at the time of the arrest showed ventricular fibrillation with possible torsades rhythm. Return of spontaneous circulation was achieved after cardiac resuscitation with cardioversion and magnesium, and epinephrine injections. Prior to the event, her ECG was normal and she received a single dose of ondansetron. Echocardiogram and ECG in the intensive care unit showed no signs of ischemia. The patient recovered in the ICU and she was neurologically intact at the time of the report. • Subject (b) (6) presented to the emergency room (ER) after experiencing a presyncopal episode while in the clinic waiting room. She had received 500 mg of AG-120 per day for 63 days. An ECG obtained in the ER showed normal sinus rhythm. A chest x-ray showed worsening bilateral pulmonary opacities and bilateral layering pleural effusion, right greater than left. The subject's condition improved with intravenous (IV) fluids and red blood cell transfusion. In Study 120-C-002, 5 subjects, (b) (6) (b) (6) developed seizures secondary their underlying tumors. One of the 5 subjects (Subject (b) (6) did not receive AG-120. None of the events were considered related to study drug administration by the Investigator.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESEN
06/07/2018

MOH JEE NG
06/07/2018

DALONG HUANG
06/07/2018

MOHAMMAD A RAHMAN
06/07/2018

JOSE VICENTE RUIZ
06/07/2018

MICHAEL Y LI
06/07/2018

CHRISTINE E GARNETT
06/07/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 17, 2018
Requesting Office or Division:	Division of Hematology Products
Application Type and Number:	NDA 211192
Product Name and Strength:	Tibsovo (ivosidenib) Tablets 250 mg
Applicant/Sponsor Name:	Agios Pharmaceuticals Inc.
FDA Received Date:	May 16, 2018
OSE RCM #:	2017-2613-1
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels for Tibsovo (ivosidenib) Tablets (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] In addition, the Applicant submitted the container label for a 14 count (b) (4) In their submission, Agios noted that the container for Tibsovo will be square bottle where the barcode has a flat surface; therefore, the ability to scan would not be an issue due to curvature. Therefore, Agios requests to keep the bar code orientation in a horizontal position for the 60-count bottle.

2 CONCLUSION

The revised container labels for Tibsovo are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rahimi, L. Label and Labeling Review for Tibsovo (ivosidenib) Tablets (NDA 211192). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 03. RCM No.: 2017-1613.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEEZA RAHIMI
05/18/2018

HINA S MEHTA
05/18/2018

CLINICAL INSPECTION SUMMARY

Date	May 11, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kelly Norsworthy, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Laura Wall M.Sc., Regulatory Project Manager Division of Hematology Products
NDA	211192
Applicant	Agios Pharmaceuticals, Inc.
Drug	ivosidenib (AG-120)
NME	Yes
Therapeutic Classification/Status	Inhibitor of the isocitrate dehydrogenase 1 (IDH1) mutant protein
Proposed Indication	Relapsed or refractory acute myeloid leukemia (R/R AML)
Consultation Request Date	January 11, 2018
Summary Goal Date	May 14, 2018
Action Goal Date	July 20, 2018
PDUFA Date	August 21, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical sites (Drs. Hagop Kantarjian, Eytan Stein, Richard Stone, and Stephanie de Botton) were selected by the Division of Hematology Products (DHP) for inspection in support of NDA 211192. The sponsor, Agios Pharmaceuticals, Inc., was also inspected. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.

The final regulatory compliance classification for Drs. Kantarjian and Stone, and sponsor is No Action Indicated (NAI). The preliminary regulatory classification of Dr. de Botton is No Action Indicated (NAI). The final regulatory classification for Dr. Stein is Voluntary Action Indicated (VAI).

2. BACKGROUND

Ivosidenib (AG-120) is a potent inhibitor of the isocitrate dehydrogenase 1 (IDH1) mutant protein. Ivosidenib has been evaluated for its potential to inhibit binding and enzymatic activity in a panel of 80 receptors, ion channels, and enzymes. Ivosidenib is selective with no significant off-target activity observed. As per the sponsor's report, this drug has been shown to inhibit alpha-ketoglutarate (α-KG) activity causing suppression of 2-hydroxyglutarate (2_HG) formation and is a proposed treatment for patients with advanced hematologic malignancies, specifically in subjects with relapsed or refractory acute myeloid leukemia (R/R AML) with an IDH1 mutation.

Study AG120-C-001
AG120-C-001 is an ongoing Phase 1, multicenter, open-label, dose escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity evaluation of orally administered ivosidenib (AG-120) in subjects with advanced hematologic malignancies with an IDH1 mutation. The primary study objectives were: (a) to assess the safety and tolerability of treatment with AG-120 administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced hematologic malignancies, (b) to determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of AG-120 in subjects with advanced hematologic malignancies, and (c) to assess the clinical activity of AG-120 in subjects with relapsed and/or refractory (R/R) acute myelogenous leukemia (AML) with an IDH1 mutation who are enrolled in Arm 1 of the expansion phase.

The dose escalation portion consisted of patients who had relapsed or refractory AML, and myelodysplastic syndrome with refractory anemia with excess blasts, or considered high-risk by the Revised International Prognostic Scoring System (IPSS-R). During the expansion portion, 4 non-randomized arms with IDH1-mutated hematologic malignancies were enrolled.

A total of 258 subjects across 25 study screening centers have been administered AG-120 during the dose escalation and expansion portions of Study AG120-C-001 across 5 dosing cohorts. A total of 179 subjects in the Full Analysis Set (FAS) had R/R AML and starting dose was 500 mg QD; of these, 159 were included in the Arm 1+ subset, of whom 125 received their first dose of AG-120 at least 6 months prior to the data cut-off date of May 12, 2017. These subjects comprise the primary efficacy analysis set (Arm 1+ subjects in FAS1).

The primary analysis of the clinical activity of AG-120 for R/R AML was on Complete Remission + Complete Remission with partial hematologic recovery (CR+CRh) rate, where CR was based on Investigator assessment of response and CRh was derived by the Sponsor from relevant data, including Investigator-collected bone marrow and hematology data from responders. The primary efficacy analysis would have occurred at the time when at least 125 Expansion Arm 1 AML subjects (including Arm 1 eligible subjects from dose escalation whose starting dose was 500 mg QD) have completed at least 6 months of treatment or discontinued study drug earlier.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects treated	Inspection Dates	Classification
Hagop Kantarjian, M.D. The University of Texas M.D. Anderson Cancer Center Department of Leukemia Unit 428 1515 Holcombe Blvd. Houston, TX 77030	AG120-C-001 Site # 511 49 total	March 12-16, 2018	NAI
Eytan Stein, M.D. Memorial Sloan Kettering Cancer Center 1275 York Ave. New York, NY 10065	AG120-C-001 Site 504 30 total	February 20 to 27, 2018	VAI
Richard Stone, M.D. Dana Farber Cancer Institute 450 Brookline Ave. Boston, MA 02115 AND Massachusetts General Hospital 55 Fruit St. Boston, MA 02115	AG120-C-001 Site 503 and Site 901 27 total (21 at DFCI plus 6 at MGH)	February 12 to 20, 2018	NAI
Stephanie de Botton, M.D. Institut Gustave Roussy Service Sitep 114 Rue Edouard Vaillant Villejuif Cedex 94805 France	AG120-C-001 Site 701 29 total	April 23 to 26, 2018	Preliminary: NAI
Agios Pharmaceuticals, Inc. 88 Sidney St. Cambridge, MA 02139	Study AG120-C-001	March 1 to 9, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Hagop Kantarjian, MD

A total of 54 subjects were screened and 49 subjects were treated. The study is ongoing. A review of 35 treated subjects' records at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for 35 treated subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Eytan Stein, M.D.

A total of 36 subjects were screened, and 30 subjects were treated. The study is ongoing. An audit of 30 treated subjects' records at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for the 30 treated subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice, however a Form FDA 483 was issued for not following the investigational plan and inadequate documentation of concomitant medications.

Protocol violations included late reporting of SAEs in three study subjects: Subject # (b) (6) (dyspnea), Subject # (b) (6) (colitis and sepsis) and Subject # (b) (6) (anemia and pleural effusion). The late SAEs were reported to the Sponsor and included in the NDA data listings. These were considered protocol deviations. Additionally, for Subject # (b) (6), AEs of atrial fibrillation, grade 2 and peripheral edema, grade 3 were noted in source toxicity grading records, but were not found in the subject's e-CRFs.

The observation regarding inadequate documentation of concomitant medications included: Subject # (b) (6) (amiloride/diuretic), Subject # (b) (6) (tramadol and oxycodone/pain, metoprolol), and Subject # (b) (6) (acyclovir/viral prophylaxis). These findings were isolated for these subjects receiving multiple medications for their serious illnesses.

Dr. Stein responded adequately to the issued Form FDA 483 on March19, 2018. In his response, Dr. Stein also mentioned that the AEs for Subject (b) (6) will be reported by MSKCC leukemia service research staff, at the reopening of this ongoing study's database for the 2018 third quarter data update.

3. Richard Stone, M.D.

This clinical investigator site had a total of 27 treated study subjects. A total of 32 subjects at DFCI were screened, and 21 subjects were treated. A total of 10 subjects at MGH were screened and six subjects were treated. The study is ongoing. An audit of the screened subjects' records at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for the 27 treated subjects' whose record were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

4. Stephanie de Botton, M.D.

A total of 36 subjects were screened, and 30 subjects were enrolled. Twenty nine subjects received treatment; one subject (Subject (b) (6)) was not treated after enrollment into the study. The study is ongoing. An audit of 36 screened subjects' records at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for the 29 treated subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

Sponsor

5. Agios Pharmaceuticals, Inc.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring

plans; monitoring reports; safety reports; adverse events; protocol deviations; and standard operating procedures. A total of three study sites were chosen for review of records, Drs. Kantarjian (MDACC), Dr. Stein (MSKCC), and Dr. de Botton (Paris, France).

Clinical site monitoring was performed by (b) (4), a contract research organization (CRO). Monitoring reports indicated that the sites received adequate periodic monitoring by the CRO. There was no under-reporting of serious adverse events by the sponsor.

In general, this sponsor appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
05/11/2018

JANICE K POHLMAN
05/11/2018

KASSA AYALEW
05/17/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 5/4/2018

To: Laura Wall, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for TIBSOVO® (ivosidenib) tablets, for oral use

NDA: 211192

In response to DHP's consult request dated January 3, 2018, OPDP has reviewed the proposed product labeling (PI) for TIBSOVO® (ivosidenib) tablets, for oral use

PI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on April 20, 2018 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be submitted under separate cover.

(b) (4) **Container Labeling**: OPDP has reviewed the proposed (b) (4) container labeling submitted by the Sponsor and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

Section	Statement from Draft (if applicable)	OPDP Comment
2.2 Recommended Dosage	"Administer TIBSOVO (b) (4)	OPDP recommends revising to include (b) (4)
17 Patient Counseling Information	(b) (4)	(b) (4)

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RACHAEL E CONKLIN
05/04/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 2, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TIBSOVO (ivosidenib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 211192
Applicant:	Agios Pharmaceuticals Inc.

1 INTRODUCTION

On December 21, 2017, Agios Pharmaceuticals Inc., submitted for the Agency's review a 505(b)(1) New Drug Application (NDA) 211192 for TIBSOVO (ivosidenib) tablets, for oral use. The proposed indication for TIBSOVO (ivosidenib) tablets is for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on January 3, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TIBSOVO (ivosidenib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TIBSOVO (ivosidenib) tablets MG received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 20, 2018.
- Draft TIBSOVO (ivosidenib) tablets Prescribing Information (PI) received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 20, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN W REDWOOD
05/02/2018

RACHAEL E CONKLIN
05/02/2018

BARBARA A FULLER
05/02/2018

LASHAWN M GRIFFITHS
05/02/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 03, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211192
Product Name and Strength:	Tibsovo (ivosidenib) Tablets 250 mg
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Agios Pharmaceuticals Inc.
FDA Received Date:	December 21, 2017
OSE RCM #:	2017-2613
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Agios Pharmaceuticals submitted a New Drug Application (NDA 21192) for Tibsovo (ivosidenib) tablets for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase 1 (IDH1) mutation.

The Division of Hematology Products (DHP) requested DMEPA to review the Prescribing Information (PI), Medication Guide, and container labeling of the product for areas of vulnerability that may lead to medication error.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the submitted PI, Medication Guide, and container labels for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the PI and container label that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information (HPI):

1) We recommend revising the statement [redacted] to "Recommended dose is 500 mg orally once daily; [redacted] with or without food [redacted] until disease progression or unacceptable toxicity. (2.2)" to ensure this important information is not overlooked.

2) Add a second bullet with the statement "[redacted] a high-fat meal. (2.2)" to ensure this important information is not overlooked.

3) Add a third bullet with the statement "[redacted] to ensure this important information is not overlooked.

4) Consider adding a statement regarding [redacted] to ensure this important information is not overlooked. Consider adding [redacted]

4.2 RECOMMENDATIONS FOR AGIOS PHARMACEUTICAL INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels:

1. Add the statement "Dispense the enclosed Medication Guide to each patient" or a similar statement prominently on the principal display panel (PDP) per 21 CFR 208.24 (d).
2. Consider reorienting the barcode to a vertical position to improve the ability to scan the barcode. We note that the bar code is oriented horizontally. Barcodes placed in a horizontal position may not scan due to vial curvature. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tibsovo received on December 21, 2017 from Agios Pharmaceuticals.

Table 2. Relevant Product Information for Tibsovo	
Initial Approval Date	N/A
Active Ingredient	ivosidenib
Indication	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) wit an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.
Route of Administration	Oral
Dosage Form	Tablets
Strength	250 mg
Dose and Frequency	500 mg once daily with or without food until disease progression or unacceptable toxicity.
How Supplied	Bottles of 60 count
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 31, 2017, we searched DMEPA's previous reviews using the terms, Tibsovo. Our search identified zero labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Tibsovo labels and labeling submitted by Agios Pharmaceuticals.

- Container label received on December 21, 2017
- Medication Guide received on December 21, 2017
- Prescribing Information (Image not shown) received on December 21, 2017

G.2 Label and Labeling Images

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEEZA RAHIMI
04/04/2018

HINA S MEHTA
04/05/2018