THE LANCET
Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Abou-Alfa GK, Macarulla T, M Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; published online May 13. http://dx.doi.org/10.1016/S1470-2045(20)30157-1.

Supplementary Appendix

Ivosidenib in *IDH1*-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Contents

Principal investigators

The following investigators participated in this study, which was conducted across 49 sites in six countries.

France (four sites): Christophe Borg, MD, PhD; Marianne Fonck, MD; David Malka, MD; Marc Pracht, MD.

Italy (three sites): Massimo Aglietta, MD; Luca Gianni, MD; Lorenza Rimassa, MD.

South Korea (six sites): Hye Jin Choi, MD; Kyu-Pyo Kim, MD; Myung-Ah Lee, MD, PhD; Woo Jin Lee, MD; Do-Youn Oh, MD; Joon Oh Park, MD.

Spain (five sites): Jorge Adeva Alfonso, MD; Antonio Cubillo Gracián, MD; Teresa Macarulla, MD, PhD; Andres Muñoz Martin Sr., MD, PhD; Fernando Rivera Sr., MD, PhD.

United Kingdom (five sites): David Anthoney, MD; John Bridgewater, BA, MBBS, MD, PhD; Roopinder Gillmore, MD; Daniel Palmer, BSc, MBBS, PhD; Juan Valle, MD.

United States of America (26 sites): Ghassan Abou-Alfa, MD, MBA; Susan Bates, MD; Muhammad Beg, MD; Johanna Bendell, MD; Mitesh Borad, MD; Daniel Catenacci, MD; James Cleary, MD, PhD; Farshid Dayyani, MD; Vikas Dembla, MD; Crystal Denlinger, MD; Anthony El-Khoueiry, MD; Ignacio Garrido-Laguna, MD; Laura Goff, MD; Thorvardur Halfdanarson, MD; William P. Harris, MD; Milind Javle, MD; Aparna Kalyan, MD; Robin Kate Kelley, MD; Daneng Li, MD; Sam J. Lubner, MD; Kabir Mody, MD; Adrian G. Murphy, MD, PhD; Vaibhav Sahai, MD; Rachna T. Shroff, MD; Davendra Sohal, MD; Benjamin Tan Jr., MD ; Andrew Zhu, MD, PhD.

Principal Investigator (s)	Site	Country	Total patients randomised
Shroff, Rachna T*/ Milind, Javle	The University of Texas MD Anderson Cancer Center	United States	14
Abou-Alfa, Ghassan	Memorial Sloan-Kettering Cancer Center	United States	13
Kelley, Robin Kate	University of California San Francisco-Helen Diller Family Comprehensive Cancer Center	United States	10
Lubner, Sam	University of Wisconsin Carbone Cancer Center	United States	9
Cleary, James	Dana Farber Cancer Institute	United States	8
Catenacci, Daniel	University of Chicago Medical Center	United States	7
Garrido-Laguna, Ignacio	Huntsman Cancer Institute at the University of Utah	United States	6
Harris, William	Seattle Cancer Care Alliance	United States	6
Murphy, Adrian	Johns Hopkins University	United States	6
Denlinger, Crystal	Fox Chase Cancer Center	United States	5
Sohal, Davendra	Cleveland Clinic Taussig Cancer Center	United States	5
Zhu, Andrew	Massachusetts General Hospital	United States	5
Bendell, Johanna	Sarah Cannon Research Institute	United States	4
Borad, Mitesh	Mayo Clinic	United States	4
El-Khoueiry, Anthony	USC Norris Cancer Center	United States	4
Goff, Laura	Vanderbilt University Medical Center	United States	4
Beg, Muhammad	University of Texas Southwestern Medical Center	United States	3
Li, Daneng	City of Hope Medical Center	United States	3

Principal Investigator (s)	Site	Country	Total patients randomised
Sahai, Vaibhav	University of Michigan	United States	3
Dembla, Vikas	Gibbs Cancer Center and Research Institute	United States	2
Mody, Kabir	Mayo Clinic-Jacksonville-FL	United States	2
Halfdanarson, Thorvardur	Mayo Comprehensive Cancer Center	United States	1
Tan, Benjamin	Washington University School of Medicine	United States	1
Bates, Susan	Columbia University Medical Center-Herbert Irving Comprehensive Cancer Center	United States	0
Dayyani, Farshid	University of California Irvine Medical Center	United States	0
Kalyan, Aparna	Northwestern University Robert H Lurie Comprehensive Cancer Center	United States	0
Bridgewater, John	University College London Hospitals (UCLH)	United Kingdom	6
Valle, Juan	Christie Hospital	United Kingdom	5
Anthoney, David	St James University Hospital	United Kingdom	0
Gillmore, Roopinder	Royal Free London NHS Foundation Trust	United Kingdom	0
Palmer, Daniel	Clatterbridge Centre for Oncology NHS Foundation Trust Clatterbridge Centre for Oncology - Wirral	United Kingdom	0
Malka, David	Institut Gustave Roussy	France	4
Borg, Christophe	Hopital Jean Minjoz	France	2
Fonck, Marianne	Institut Bergonie	France	0
Pracht, Marc	Rennes	France	0
Aglietta, Massimo	Fondazione del Piemonte per l'Oncologia FPO IRCCS	Italy	3
Rimassa, Lorenza	Istituto Clinico Humanitas	Italy	3
Gianni, Luca	Ospedale San Raffaele IRCCS	Italy	0
Macarulla, Teresa	Hospital Vall d Hebron	Spain	15
Adeva, Jorge	Hospital Universitario 12 de Octubre	Spain	8
Cubillo, Antonio	Centro Integral Oncológico Clara Campal (CIOCC)	Spain	3
Rivera, Fernando	Hospital Universitario Marques de Valdecilla	Spain	1
Munoz, Andres	HGUG Marañón	Spain	0
Oh, Do-Youn	Seoul National University Hospital	Korea	6
Kim, Kyu-Pyo	Asan Medical Center	Korea	4
Park, Joon Oh	Samsung Medical Center	Korea	2
Choi, Hye Jin	Severance Hospital, Yonsei University Health System	Korea	0
Lee, Myung-Ah	The Catholic University of Korea Seoul St Mary's Building	Korea	0
Lee, Woo Jin	National Cancer Center Hospital	Korea	0

*Rachna T Shroff moved from the University of Texas MD Anderson Cancer Center to the University of Arizona Cancer Center, which was added as a new site following her move.

Supplementary methods

Study design and treatment

ClarIDHy (AG120-C-005) is a phase 3, multicentre, double-blind safety and efficacy study of ivosidenib in patients with advanced cholangiocarcinoma. Recruitment was initiated in February 2017. As of January 31, 2019 (analysis cutoff date), 185 patients had been randomised 2:1 to ivosidenib or matched placebo. The primary analysis of progression-free survival (PFS) occurred once 131 PFS events were determined by investigator assessment. Because

the primary endpoint was statistically significant, overall survival was tested following the hierarchical testing procedure as specified in the study protocol.

An independent data monitoring committee regularly reviewed the safety data to ensure the safety of treatment and proper conduct of the study. The first interim safety review meeting occurred once approximately 20 patients had completed two cycles of treatment or had discontinued earlier. Thereafter, review meetings occurred every 3 to 6 months, or on an ad hoc basis. No formal interim analysis for efficacy was conducted before the primary analysis.

Each patient's course of treatment consisted of the following periods:

Pre-screening period (optional): *IDH1* mutation status by central laboratory testing as part of the patient's eligibility for enrolment in the study. Potential participants were required to sign a pre-screening consent form. Any patient who did not provide a tumour sample for testing at pre-screening provided one at screening.

Pre-treatment/screening period: Following informed consent, all patients were screened to determine eligibility within 28 days before the start of study treatment on cycle (C) 1 day (D) 1. Radiographic scans at baseline were performed within 21 days of C1D1. Additional screening procedures included review of entry criteria; recording of demographics and disease history; medical, surgical, and medication history; radiographic evaluation to determine extent of disease; and complete physical examination.

Treatment period and end-of-treatment visit: Upon meeting all eligibility criteria and following randomisation, daily study treatment began on C1D1. Cycles were 28 days long (±2 days) and dosing was continuous. All patients continued to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. An end-of-treatment (EOT) visit was scheduled on the last day of study treatment within 5 to 33 days of the last dose to accommodate for potential dosing delays of up to 28 days. For patients who discontinued the study for reasons other than disease progression or start of another anticancer agent, an assessment was conducted at the EOT visit.

An overview of the study design and course of treatment is provided in figure S1. The complete protocol is available at the end of the appendix.

Placebo-to-ivosidenib crossover

Upon documented disease progression (as determined by the investigator), and in consultation with the sponsor's medical monitor, patients and site staff were unblinded to treatment assignment. Placebo patients who continued to meet eligibility criteria established during the EOT visit were permitted to cross over to the active treatment group. Placebo was not considered a prior line of therapy for the purpose of eligibility. Patients who crossed over started again with study procedures as at C1D1 and continued to be evaluated for tumour response by the investigator.

Laboratory assessments

All clinical laboratory assessments were performed by the study site's local laboratory and conducted according to the specified schedule of assessments. Clinical laboratory evaluations were conducted up to 24 hours before each study visit but within the visit window (±2 days). All clinically significant laboratory abnormalities observed during testing were followed by repeat testing and further investigated at the discretion of the investigator. The laboratory parameters assessed by the investigator are summarised in table S1.

A serum pregnancy test was performed at screening and a urine pregnancy test was performed and confirmed negative on day 1 of the study before dosing and of every cycle for all female patients of child-bearing potential.

***IDH1* mutation testing**

Prior to randomisation, *IDH1* mutation status was confirmed centrally by next-generation sequencing testing in a Clinical Laboratory Improvement Amendments-certified laboratory on formalin-fixed paraffin-embedded tumour tissue using Oncomine™ Focus Assay (Thermo Fisher Scientific, Waltham, MA, USA). The five most prevalent *IDH1* R132(C/H/G/L/S) mutations in the Oncomine Focus Assay panel were validated in formalin-fixed paraffin-embedded cholangiocarcinoma tissues. The analytical performance characteristics (accuracy, sensitivity, linearity, and precision) met the expectations of and were approved by the Center for Devices and Radiological Health as a Clinical Trial Assay for the study enrolment.

The rank-preserving structural failure time (RPSFT) model

Following unblinding after documented progressive disease (PD), placebo patients who met crossover eligibility criteria were permitted to receive open-label ivosidenib. As discussed in the main text, the RPSFT model was used to reconstruct the survival time for placebo patients as if the crossover to the active treatment arm did not occur.

RPSFT models, initially developed in the early 1990s, have been used for decades to estimate treatment effect in the scenario of treatment switching in a study,[1-3] with the assumption that survival times would have been comparable in all study groups in the absence of experimental treatment because of randomisation.[2,3]

Patient-reported outcomes

Quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Cholangiocarcinoma and Gallbladder Cancer module (EORTC QLQ-BIL21); Patient Global Impression (PGI) questions adapted from the National Institute of Mental Health PGI of Change (PGI-C) for three prespecified domains of interest (physical functioning, pain, and appetite loss); and the 5-level EuroQoL-5 Dimension (EQ-5D-5L) for future health economic modelling.[4-7] Except for the EQ-5D-5L, these assessments were conducted before dosing on C1D1 and were to be recorded on the first day of every subsequent cycle until EOT. After the EOT visit, these assessments were to be conducted every 12 weeks until the start of new anticancer therapy. One additional assessment was also conducted at the safety follow-up visit (28 days or up to 33 days after the last dose of study drug). EQ-5D-5L assessments were to occur before dosing on C1D1, C3D1, and at the EOT visit. The original trial protocol was amended to adjust the frequency of the assessments and add PGI questions.

Mixed-effect models with repeated measurements were conducted on the change from baseline across visits for each key EORTC QLQ-C30 and QLQ-BIL21 subscale pertaining to the prespecified domains of interest, with baseline score, treatment, visit, and treatment-by-visit as fixed effects and patient as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used.

Estimation of clinically meaningful change thresholds was achieved by computing the change scores for the EORTC QLQ-C30 and QLQ-BIL21 subscale scores relating to the domains of interest (see below) between baseline (C1D1) and C2D1, associated with meaningful change using 7-level PGI-C ratings as anchors. The focus was on C2D1 considering the availability of QoL data. Meaningful worsening was defined as any worsening based on the PGI-C (ie, “A little worse”, “Moderately worse”, or “Very much worse”), and meaningful improvement was defined as any improvement based on the PGI-C (ie, “A little better”, “Moderately better”, or “Very much better”). Relevant subscales of the EORTC QLQ-C30 and QLQ-BIL21 were paired with their corresponding PGI-C ratings as anchors: the physical functioning PGI-C was employed for the EORTC QLQ-C30 Physical Functioning subscale, the EORTC QLQ-C30 and QLQ-BIL21 Pain Symptom subscales were each paired with the Pain PGI-C, and the EORTC QLQ-C30 Appetite Loss and QLQ-BIL21 Eating Symptom subscales were paired with the Appetite Loss PGI-C.

Supplementary results

Patients

At the time of the data cutoff date for this analysis, 35 of 61 patients randomised to placebo had crossed over to the ivosidenib treatment arm. Of the remaining 26 patients, 13 were assigned “death” as the reason for not having crossed over. However, it should be noted that one of these 13 patients was allowed to cross over but was administered the wrong treatment (placebo). The patient died approximately 1 month later. This patient was considered a non-crossover patient as they had never received ivosidenib.

Clinical efficacy

PFS by investigator assessment

The PFS result by central review was further supported by the “PFS result by local review”, which was also statistically positive and favoured ivosidenib (HR=0·47 [95% CI 0·33–0·68]; median PFS 2·7 months [95% CI 1·6–3·6] *vs* 1·4 months [1·4–2·5], p<0·0001). The PFS rates at 6 and 12 months for ivosidenib patients were 32% and 10%, respectively, compared with 4% at 6 months and 0% at 12 months for those receiving placebo. The Kaplan-Meier curve for “PFS by investigator assessment” is shown in figure S2.

PFS after crossover

A total of 35 patients crossed over from placebo to ivosidenib as of the data cutoff date. The “PFS duration by investigator assessment” in the crossover population before and after crossover is shown in figure S3. Nine (26%) of the 35 crossover patients were censored at the time of this analysis, with eight patients remaining on placebo.

Overall survival across subgroups
The treatment effect on overall survival across subgroups at the time of primary analysis is shown in figure S4.

Overall response
The best overall responses per independent radiology centre (IRC) before crossover and the best overall responses per investigator before and after crossover are summarised in tables S2 and S3. The objective response rate for ivosidenib by IRC before crossover was 2% (n=3). As of the analysis cutoff date, the maximum treatment duration for patients on ivosidenib was 22·5 months, with the majority of patients experiencing a durable stable disease (SD). Ivosidenib resulted in a greater disease control rate (partial response [PR]+SD) of 53% (n=66, including three PRs) compared with placebo, where SD was documented in only 28% of patients (n=17). More placebo patients (n=35; 57%) experienced PD as the best overall response compared with those receiving ivosidenib (n=41; 33%). The best percentage change from baseline in target legion measurements by central review in the intention-to-treat population is shown in figure S5.

The three patients who achieved PRs had treatment durations of 11·0, 6·0, and 17·1 months, respectively, with duration of PR of 2·8, 2·7, and 11·0 months, respectively. The patient with the longest treatment duration was still receiving ivosidenib, and the other two patients had discontinued ivosidenib due to PD as assessed by the investigator (table S4). The time to response for these three patients was, respectively, 8·3, 2·8, and 5·5 months. Two of the three patients on ivosidenib who achieved a confirmed PR by IRC also achieved a confirmed PR by investigator assessment. The swim lane plot of treatment duration and response per investigator in the intention-to-treat population is shown in figure S6.

Safety

Common adverse events (AEs) and treatment-related AEs
Table S5 presents an expanded list of treatment-emergent AEs (TEAEs) that occurred in ≥5% (all grades) or ≥1% (grade 3 or above) of patients who received at least one dose of ivosidenib, including those who crossed over to the active treatment arm from placebo. AEs after crossover were similar to those reported before crossover, with only minor numerical differences. Table S6 lists all treatment-related AEs reported in ≥5% (all grades) or ≥1% (grade 3 or above) of patients who received at least one dose of ivosidenib, including placebo-to-ivosidenib crossover patients.

Patients receiving placebo experienced more TEAEs (all grades) compared with patients receiving ivosidenib, when adjusted for the total drug exposure time in each treatment arm (42·0 TEAEs per person-year [95% CI 38·1–46·3] *vs* 27·7 TEAEs per person-year [95% CI 26·2–29·4], respectively). Of note, gastrointestinal disorders overall were more common among patients on placebo than among those on ivosidenib (11·7 TEAEs per person-year [95% CI 9·7–14·0] *vs* 7·6 TEAEs per person-year [95% CI 6·8–8·5], respectively). This observation is consistent with symptoms related to progression of the underlying disease, which occurred more rapidly on placebo than ivosidenib.

On-treatment deaths
The majority of reported on-treatment deaths (24 of 30 deaths) resulted from disease progression and comprised ten patients receiving placebo and 14 patients receiving ivosidenib. The remaining six patients (four patients initially assigned to the treatment group and two allowed to cross over upon disease progression) experienced TEAEs leading to on-treatment death. These TEAEs included intestinal obstruction, intestinal pseudo-obstruction, hepatic cirrhosis, pneumonia, sepsis, and pulmonary embolism. Additional details for these six patients are provided in table S7.

Patient-reported outcomes
For the EORTC QLQ-C30, higher function-related scores represent better level of functioning and QoL. By mixed-effect models with repeated measurements analysis, the decline from baseline at C2D1 on the EORTC QLQ-C30 Physical Functioning subscale was significantly greater for patients in the placebo arm versus those in the ivosidenib arm (figure S7 and table S8).

All patients who self-reported that their physical functioning had worsened at C2D1 via the PGI-C anchor question also showed worsening on their EORTC QLQ-C30 Physical Functioning subscale scores (n = 22, mean = -13·6, standard deviation = 16·4) compared with baseline (table S9). Comparatively, those patients reporting “No Change” or improvement on the PGI-C had virtually no change in their EORTC QLQ-C30 Physical Functioning subscale scores at C2D1 compared with baseline (“No Change” n = 25, mean = -1·1, standard deviation = 12·1; “Improved”

n = 32, mean = 0·2, standard deviation = 17·8). Further, the "No Change" group median Physical Functioning subscale change score was 0 compared with -13·3 for the worsened group. This pattern of results suggests that the Physical Functioning subscale was able to detect worsening of physical functioning in these patients but not necessarily improvements and indicates that a 12- to 13-point decrease in Physical Functioning subscale score represents clinically meaningful worsening. Based on this threshold and mixed-effect modelling of mean changes from baseline in Physical Functioning subscale score within arms (table S8), clinically meaningful decline of physical functioning was only observed in the placebo arm at C2D1.

For the EORTC QLQ-C30 symptom subscales and all QLQ-BIL21 subscales, higher scores represent worse symptoms and QoL. Significant differences in change from baseline at C2D1 between arms were not observed on pain or appetite loss subscales based on mixed-effect modelling (table S8). Clinically meaningful change thresholds could not be established for pain and appetite loss owing to data availability.

Pharmacokinetics/pharmacodynamics

Ivosidenib was rapidly absorbed following single and multiple doses, and exposure at steady state was higher than that after a single dose, with low accumulation following 28 days of daily dosing. Plasma D-2-hydroxyglutarate concentrations were elevated at baseline and decreased after both single and multiple doses of ivosidenib, whereas plasma D-2-hydroxyglutarate remained elevated on placebo (figure S8).

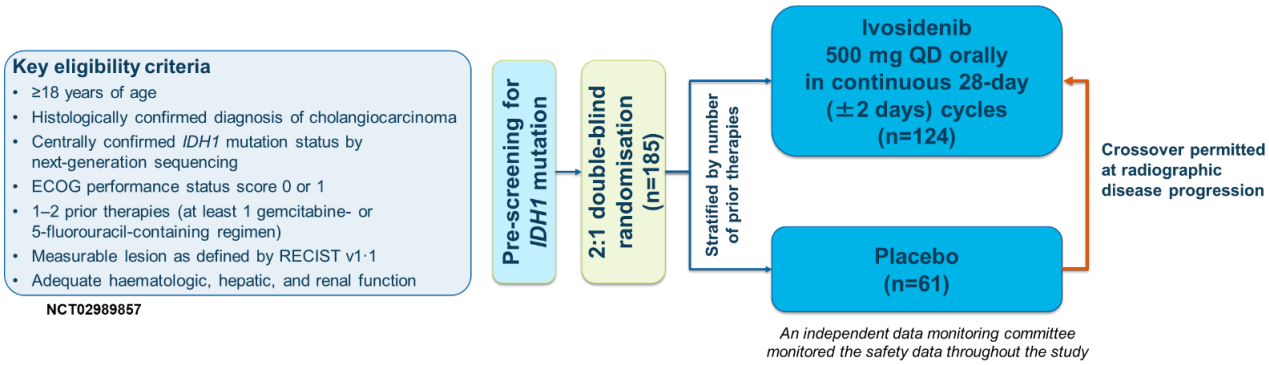


Figure S1: **Study design**
Randomised, double-blind, placebo-controlled, multicentre phase 3 trial. ECOG=Eastern Cooperative Oncology Group. QD=once daily. RECIST=Response Evaluation Criteria in Solid Tumors.

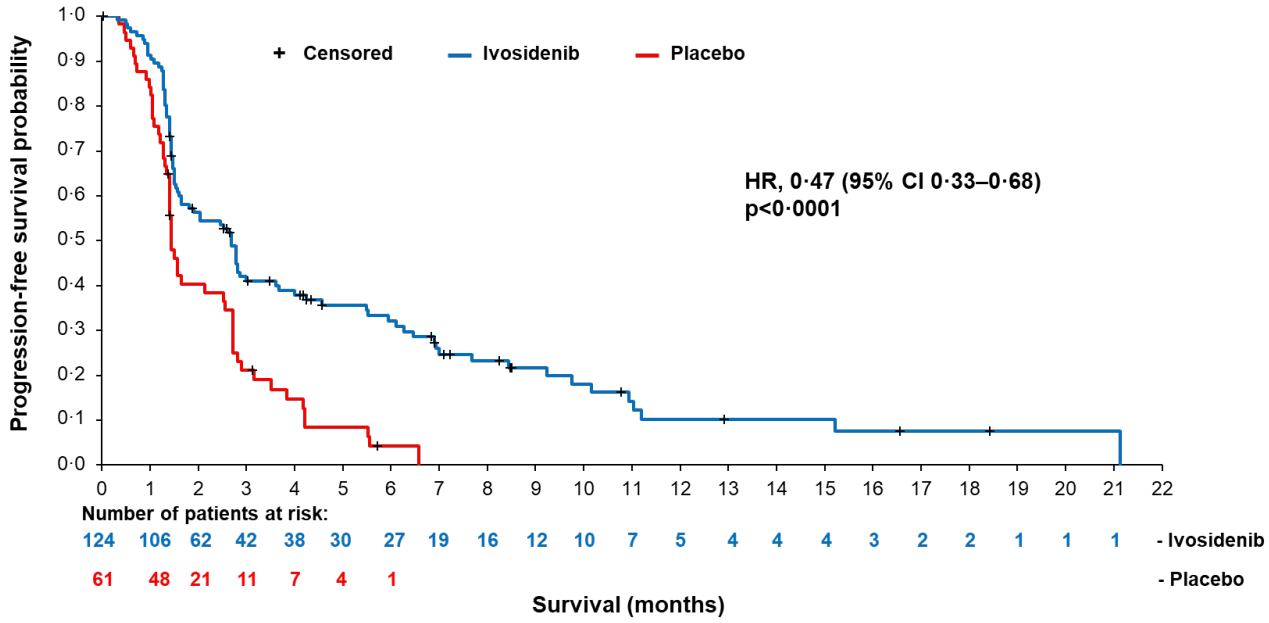


Figure S2: **Kaplan-Meier plot of progression-free survival per investigator assessment in the intention-to-treat population assigned to ivosidenib or placebo**

Patients with no baseline and no death were censored at the randomisation date. Patients starting on new anticancer therapy before progression/death were censored at the last adequate assessment prior to the new anticancer therapy. Patients without post-baseline assessment and no death were censored at the randomisation date. Patients without progression/death by the data cutoff date were censored at the last adequate assessment date. Patients with progression/death following a long gap (≥2 consecutive scheduled assessments missing) were censored at the date of the last adequate assessment prior to the gap. HR=hazard ratio.

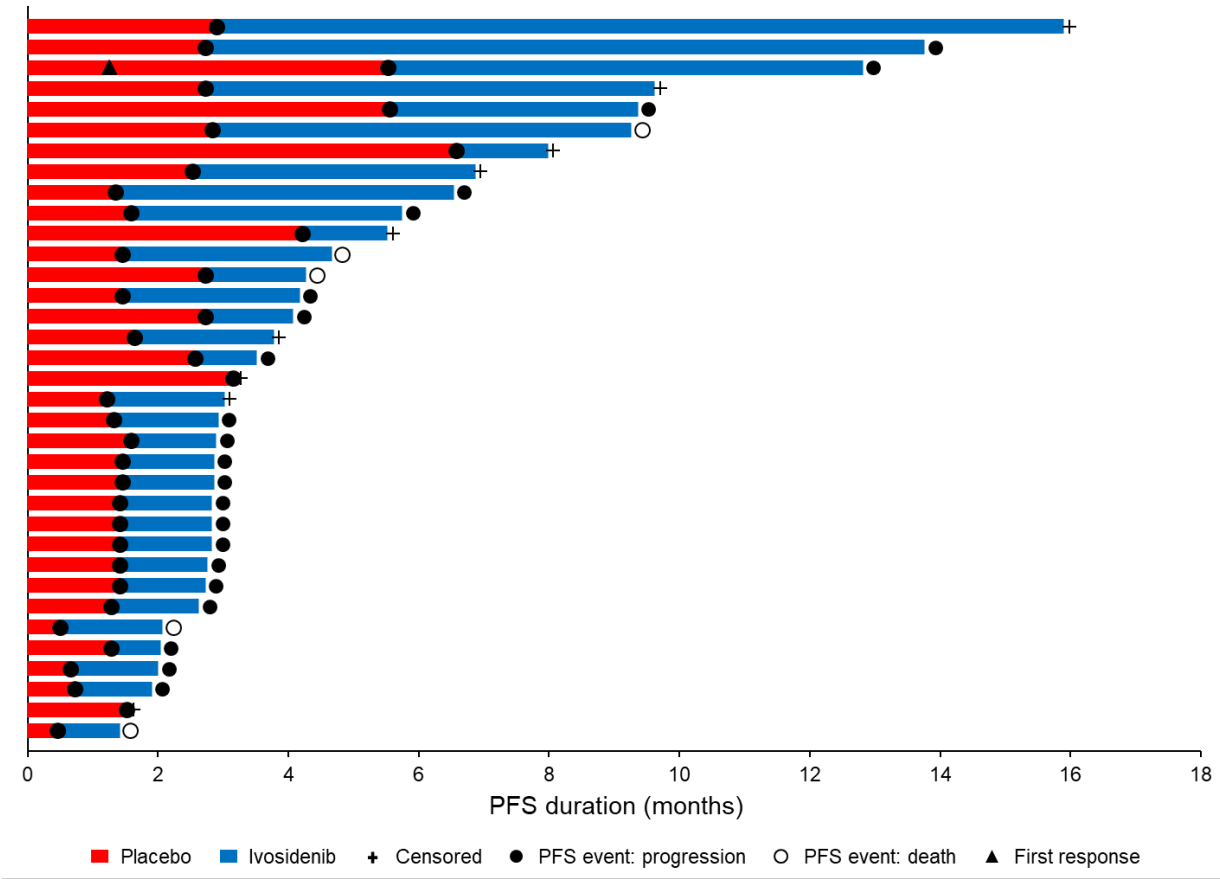


Figure S3: **PFS duration by investigator assessment for placebo-treated patients who crossed over to receive ivosidenib, before and after crossover**
Thirty-five patients crossed over from placebo to ivosidenib as of January 31, 2019, the data cutoff date; 26% of the events were censored at the time of this analysis. PFS=progression-free survival.

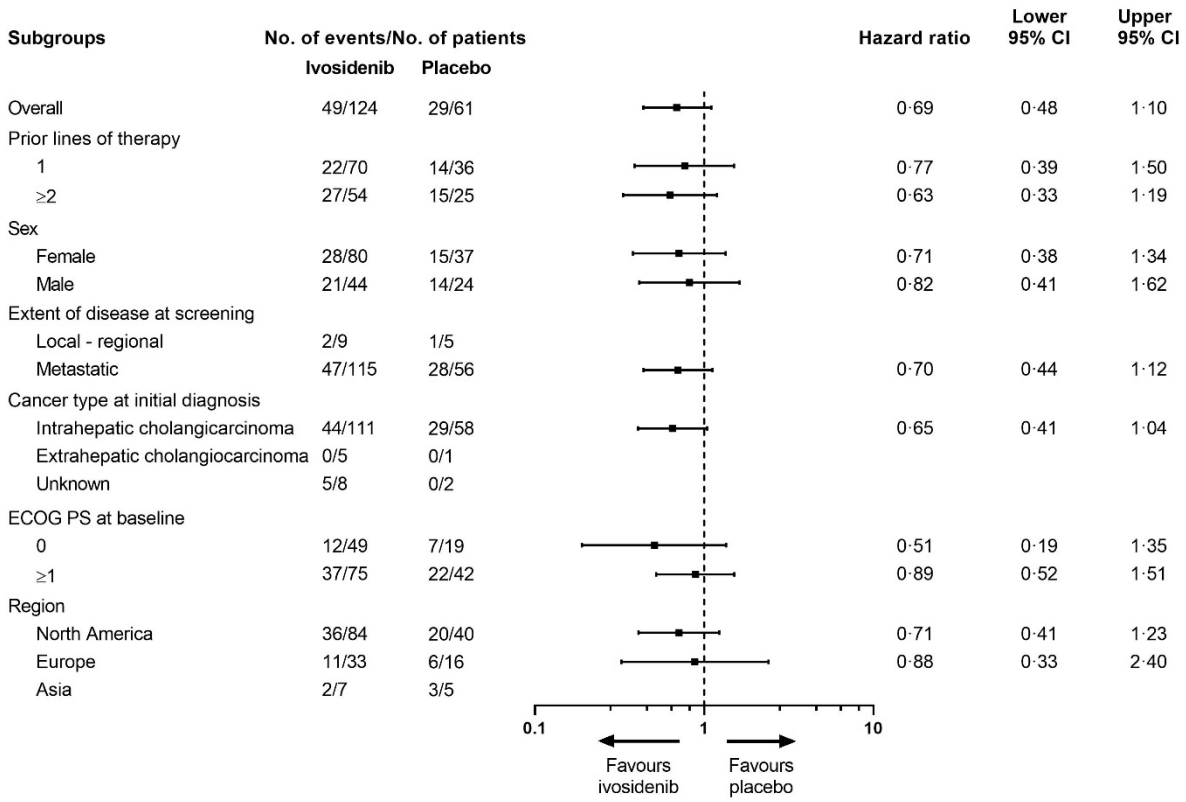
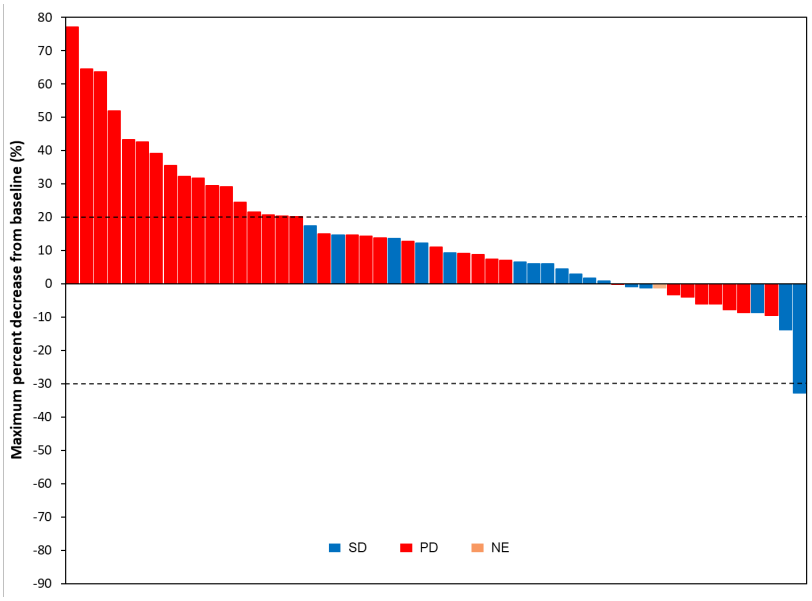


Figure S4: **Overall survival in the intention-to-treat population – forest plot by subgroup**
The HR for the "Overall" subgroup was calculated from the stratified Cox regression model with placebo as the denominator. The hazard ratio for each subgroup was calculated from the unstratified Cox regression model. Subgroups with events numbers ≤5 or number of patients ≤10 were not plotted because the small sample size would not support any robust interpretation. The number of prior lines of therapy was based on the actual prior lines that patients received per eligibility, reviewed by the sponsor's medical monitor. If patients had both local and metastatic status, disease was considered as metastatic. Perihilar disease was considered as extrahepatic disease. The baseline measurement was defined as the most recent measurement prior to the first dose of study drug. If patients were not dosed, the latest assessment was considered to be the baseline assessment. Error bars indicate two-sided 95% CIs. ECOG PS=Eastern Cooperative Oncology Group Performance Status. HR=hazard ratio.

(A) Placebo



(B) Ivosidenib

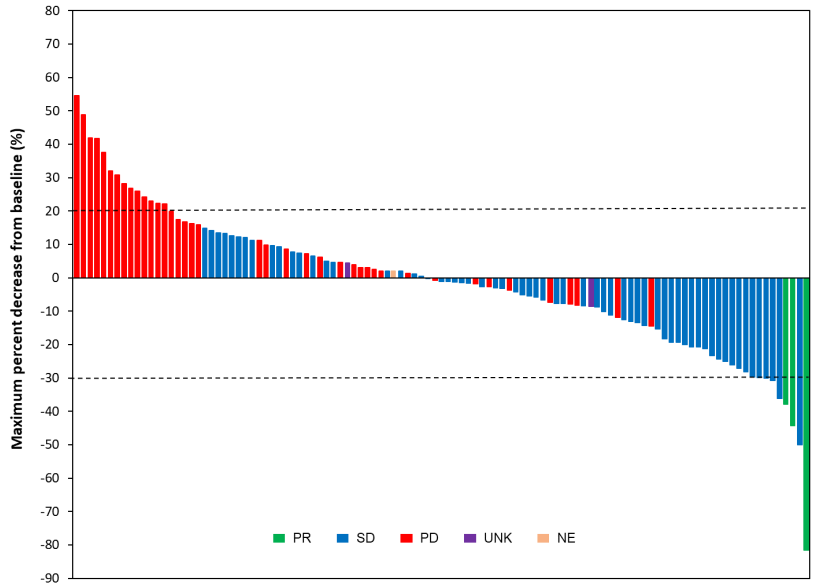
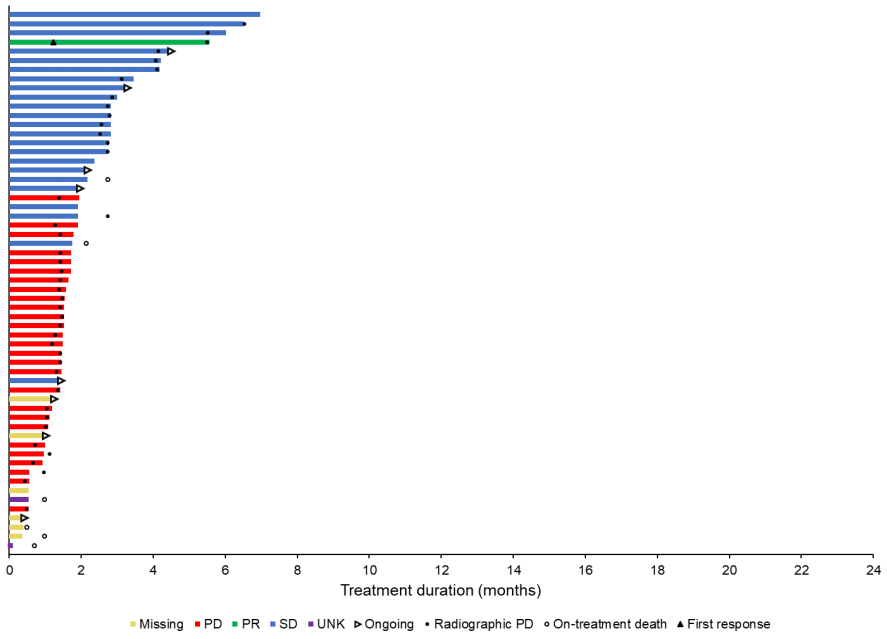


Figure S5: **Waterfall plot of best percentage change from baseline in sum of diameters for target lesion measurements by independent radiology centre assessment before crossover with (A) placebo versus (B) ivosidenib**

Colour represents the best overall response. A classification of PR required confirmation per Response Evaluation Criteria in Solid Tumors v1·1. SD occurring <38 days from the randomisation date was considered to be unknown. NE=not evaluable. PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown.

(A) Placebo



(B) Ivosidenib

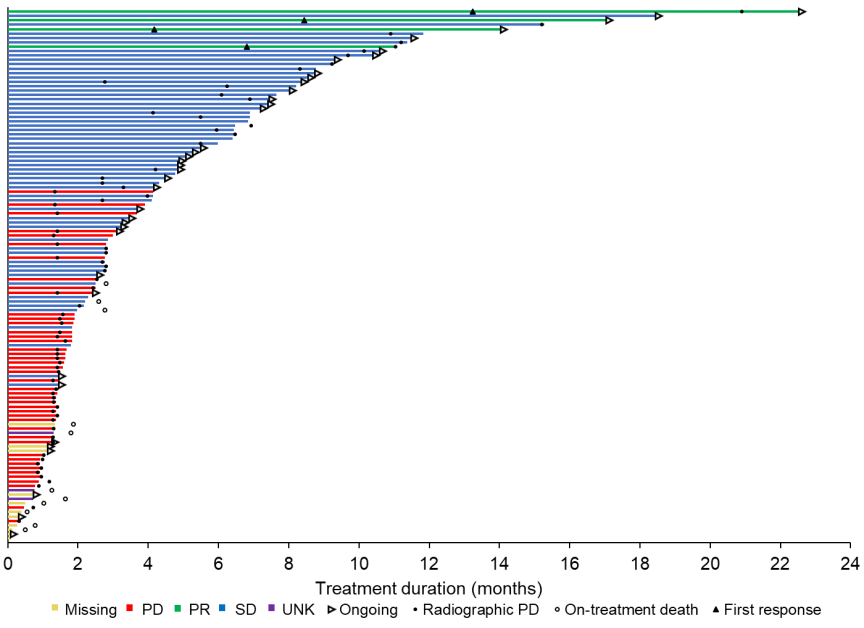


Figure S6: **Treatment duration and response by investigator assessment before crossover (in the intention-to-treat population) with (A) placebo versus (B) ivosidenib**
Colour represents the best overall response. A classification of PR required confirmation per Response Evaluation Criteria in Solid Tumors v1·1. SD occurring <38 days from the randomisation date was considered to be unknown. PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown.

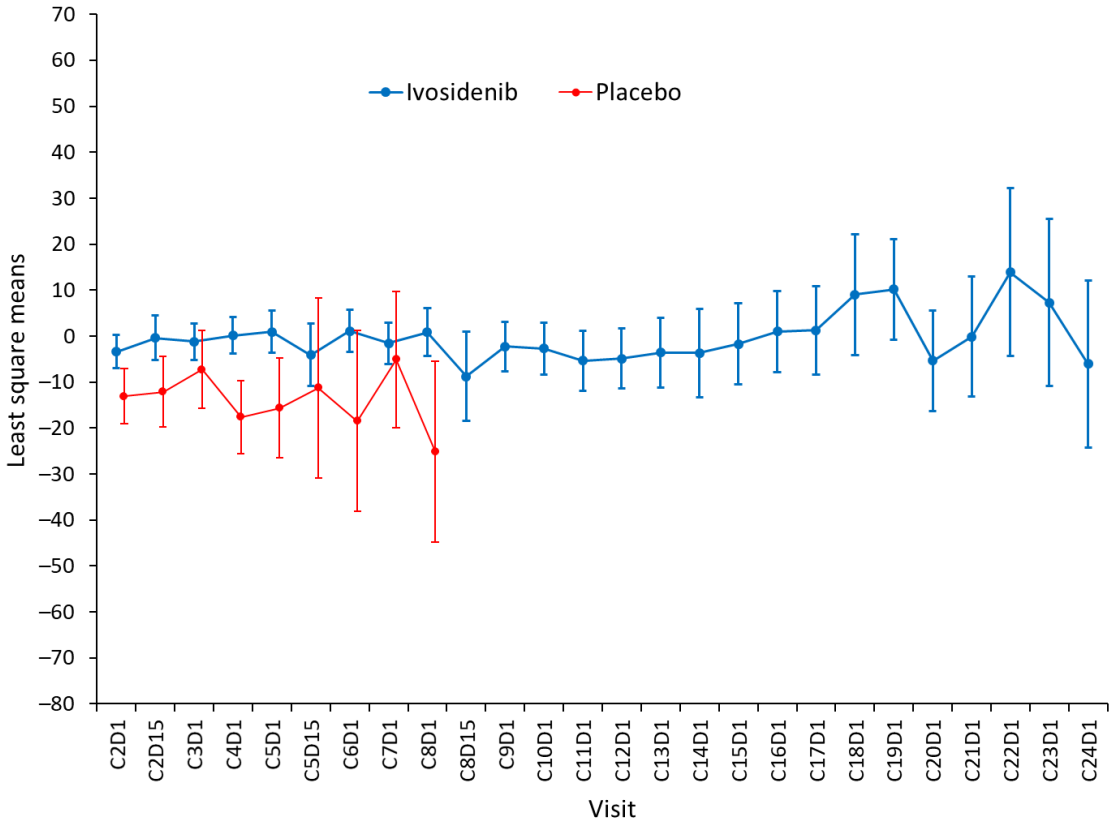


Figure S7: **EORTC QLQ-C30 physical functioning score change from baseline with ivosidenib versus placebo before crossover (in the intention-to-treat population)**

A mixed-effect model with repeated measurements on the change from baseline of the EORTC QLQ-C30 Physical Functioning subscale score was applied, with baseline score, treatment, visit, and treatment-by-visit as fixed effects, and patient as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used. 95% CI were plotted. At baseline, 113 ivosidenib and 52 placebo patients completed the assessment. At C2D1, 63 ivosidenib and 24 placebo patients completed the assessment. C=cycle. D=day. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

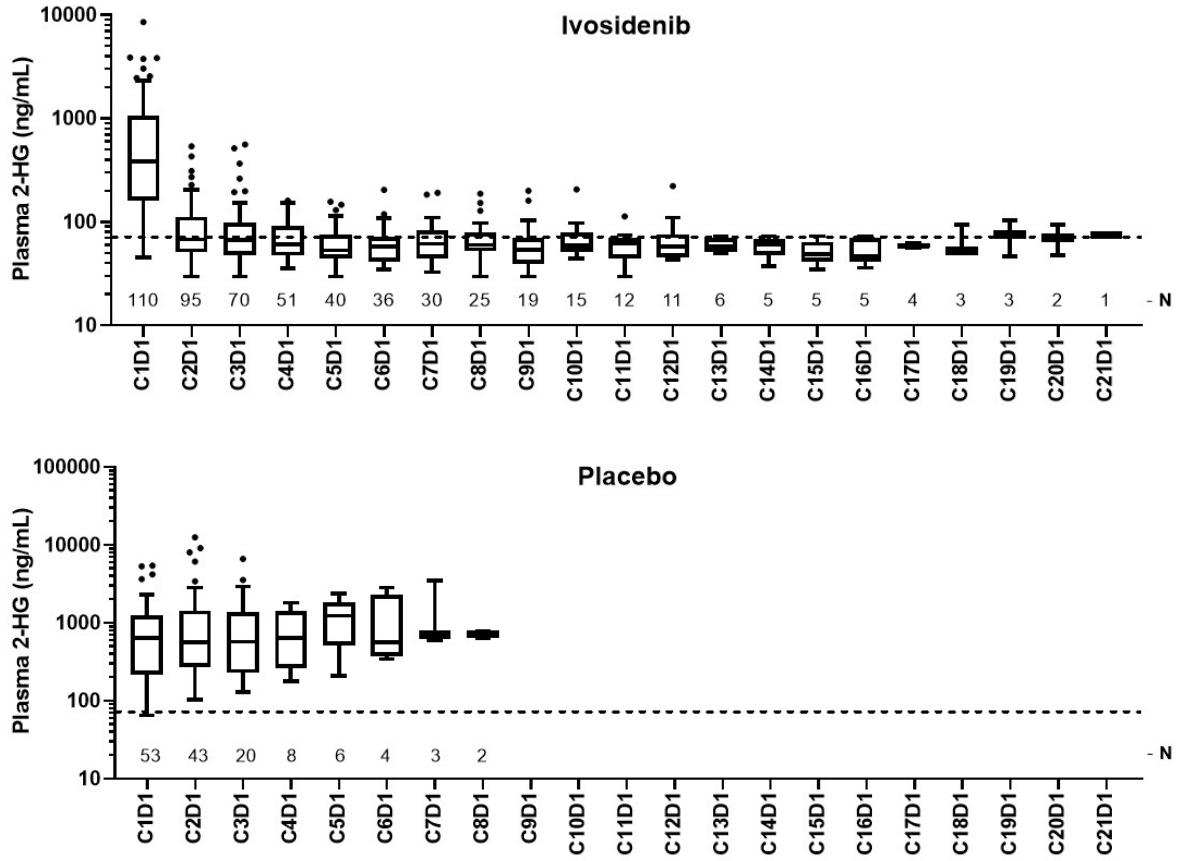


Figure S8: **Pre-dose (trough) plasma concentration of 2-HG after oral administration of ivosidenib (top panel) versus placebo (lower panel)**

The dashed line represents the mean (± standard deviation) 2-HG baseline in healthy individuals (72·6±21·8 ng/mL; standard deviation not shown).[8] Boxes indicate 25th percentile, median, and 75th percentile. Whiskers plotted using Tukey's method. C=cycle. D=day. 2-HG=D-2-hydroxyglutarate.

Table S1: **Clinical laboratory parameters evaluated by the investigator**

Haematology	Haemoglobin, red blood cell count, white blood cell count and differential (percent neutrophils, percent bands), and platelet count
Chemistry	Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen, creatinine, uric acid, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and direct bilirubin
Coagulation studies	Prothrombin time, activated partial thromboplastin time, and international normalised ratio
Urinalysis	Colour and appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic inspection of sediment

Table S2: **Summary of best overall responses per independent radiology centre before crossover (in the intention-to-treat population)**

	Ivosidenib (n=124)	Placebo (n=61)
Responses		
Confirmed best overall response, n (%)		
PR	3 (2)	0
SD	63 (51)	17 (28)
PD	41 (33)	35 (57)
UNK	2 (2)	0
NE	1 (1)	1 (2)
Confirmed objective response rate (CR or PR), n (%)	3 (2)	0
95% CI of response rate*	(0·5 to 6·9)	(0·0 to 5·9)
Odds ratio (95% CI)†	NE (0·29 to NE)	··
p value‡	0·299	··
Confirmed + unconfirmed PR, n (%)	6 (5)	0

CR=complete response. NE=not evaluable. PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown.

*Two-sided 95% CIs were calculated using the exact binomial method.

†Odds ratio was calculated with placebo as the control (denominator).

‡p value was calculated using a one-sided Fisher exact test.

Table S3: **Summary of best overall responses per investigator before and after crossover**

	Placebo (n=61)	**Ivosidenib (n=124)**	**Ivosidenib after crossover (n=35)**
Confirmed best overall response, n (%)			
PR	1 (2)	4 (3)	··
SD	23 (38)	59 (48)	15 (43)
PD	27 (44)	44 (35)	15 (43)
UNK	2 (3)	3 (2)	··
NE	··	··	1 (3)
Confirmed objective response rate (CR or PR), n (%)	1 (2)	4 (3)	0
95% CI of response rate*	(0·0– 8·8)	(0·9–8·1)	(0·0–10·0)
Odds ratio (95% CI)†	··	2·00 (0·19–100·11)	··
p value‡	··	0·466	··
Confirmed + unconfirmed PR, n (%)	1 (2)	5 (4)	0

CR=complete response. NE=not evaluable. PD=progressive disease. PR=partial response. SD=stable disease. UNK=unknown.

*Two-sided 95% CIs were calculated using the exact binomial method.

†Odds ratio was calculated with placebo as the control (denominator).

‡p value was calculated using a one-sided Fisher exact test.

Table S4: **Characteristics of patients receiving ivosidenib who achieved a confirmed partial response per independent radiology centre before crossover (in the intention-to-treat population)**

	Regimen (line of therapy)	Duration of last line of prior systemic therapy, months	Maximum change in target lesion, %	Duration of treatment, months	Time to response, months	Duration of response, months	Progression-free survival, months
Patient 1	Capecitabine (1); cisplatin + gemcitabine (2)	1·41	–38	11·04	8·28	2·79*	11·04*
Patient 2	Floxuridine + gemcitabine + oxaliplatin (1); floxuridine + irinotecan (2)	10·81	–44	5·98	2·79	2·73*	5·49*
Patient 3	Gemcitabine + oxaliplatin (1)	0·95	–82	17·05†	5·52	11·07*	16·56*

*Data were censored at the last adequate assessment date because there was no progression of disease by the data cutoff date.

†Patient 3 was still receiving treatment at the data cutoff date.

Table S5: **TEAEs reported in ≥5% (all grades) or ≥1% (grade ≥3) of patients who received at least one dose of ivosidenib (total ivosidenib)**

	Ivosidenib (n=121)	Total ivosidenib (n=156*)	Placebo (n=59)
TEAE, n (%)			
All grades (≥5% of total ivosidenib patients)			
Nausea	43 (36)	50 (32)	15 (25)
Diarrhoea	37 (31)	45 (29)	9 (15)
Fatigue	32 (26)	37 (24)	10 (17)
Cough	25 (21)	30 (19)	5 (8)
Abdominal pain	26 (21)	29 (19)	8 (14)
Ascites	25 (21)	29 (19)	9 (15)
Decreased appetite	23 (19)	27 (17)	11 (19)
Anaemia	18 (15)	25 (16)	3 (5)
Vomiting	23 (19)	25 (16)	10 (17)
Constipation	15 (12)	19 (12)	10 (17)
Oedema peripheral	15 (12)	19 (12)	6 (10)
Asthenia	15 (12)	17 (11)	8 (14)
Aspartate aminotransferase increased	13 (11)	16 (10)	3 (5)
Pyrexia	15 (12)	16 (10)	6 (10)
Dyspnoea	13 (11)	15 (10)	9 (15)
Blood bilirubin increased	12 (10)	14 (9)	4 (7)
Headache	13 (11)	14 (9)	4 (7)
Alanine aminotransferase increased	10 (8)	13 (8)	1 (2)
Blood alkaline phosphatase increased	10 (8)	13 (8)	6 (10)
Hyponatraemia	12 (10)	13 (8)	7 (12)
Abdominal distension	11 (9)	11 (7)	5 (8)
Back pain	10 (8)	11 (7)	5 (8)
Electrocardiogram QT prolonged	11 (9)	11 (7)	1 (2)
Insomnia	9 (7)	11 (7)	3 (5)
Weight decreased	7 (6)	11 (7)	2 (3)
Hypokalaemia	9 (7)	10 (6)	3 (5)
Rash	8 (7)	10 (6)	0
Abdominal pain upper	7 (6)	9 (6)	1 (2)
Arthralgia	7 (6)	9 (6)	4 (7)
Hyperglycaemia	7 (6)	9 (6)	1 (2)
Hypoalbuminemia	7 (6)	9 (6)	4 (7)
Hypomagnesaemia	8 (7)	9 (6)	3 (5)
White blood cell count decreased	8 (7)	9 (6)	1 (2)
Hyperbilirubinemia	6 (5)	8 (5)	0
Hyperkalaemia	6 (5)	8 (5)	5 (8)
Neuropathy peripheral	8 (7)	8 (5)	0
Grade ≥3 (≥1% of total ivosidenib patients)			
Ascites	9 (7)	12 (8)	4 (7)
Blood bilirubin increased	7 (6)	9 (6)	1 (2)
Anaemia	4 (3)	8 (5)	0
Aspartate aminotransferase increased	6 (5)	8 (5)	1 (2)
Hyponatremia	6 (5)	7 (4)	6 (10)
Hypophosphatemia	3 (2)	4 (3)	3 (5)
Blood alkaline phosphatase increased	3 (2)	3 (2)	3 (5)

TEAE=treatment-emergent adverse event.

*All patients who have ever been dosed with ivosidenib, including 35 placebo patients who crossed over upon radiographic progression of disease.

Table S6: **TRAEs reported in ≥5% (all grades) or ≥1% (grade ≥3) of patients who received at least one dose of ivosidenib (total ivosidenib)**

	Ivosidenib (n=121)	Total ivosidenib (n=156*)	Placebo (n=59)
TRAE, n (%)			
Any TRAE	76 (63)	92 (59)	22 (37)
Any serious TRAE	3 (2)	3 (2)	0
Most common TRAEs (≥5% of total ivosidenib patients)			
Diarrhoea	25 (21)	31 (20)	5 (8)
Nausea	25 (21)	29 (19)	9 (15)
Fatigue	19 (16)	21 (13)	4 (7)
Vomiting	11 (9)	12 (8)	7 (12)
Headache	9 (7)	9 (6)	1 (2)
Decreased appetite	8 (7)	8 (5)	4 (7)
Grade ≥3 (≥1% of total ivosidenib patients)			
Any grade ≥3 TRAE	7 (6)	10 (6)	0
Most common grade ≥3 TRAEs			
Anaemia	1 (1)	2 (1)	0
Fatigue	2 (2)	2 (1)	0
Hypophosphatemia	2 (2)	2 (1)	0

TRAE=treatment-related adverse event.

*All patients who have ever been dosed with ivosidenib, including 35 placebo patients who crossed over upon radiographic progression of disease.

Table S7: **Characteristics of patients on ivosidenib who experienced TEAEs leading to death (not related to study drug)**

	Age, years/sex	TEAE	Initial diagnosis Cancer type/grade	Treatment duration, days
Ivosidenib before crossover				
Patient 1	69/F	Infections and infestations/pneumonia	Intrahepatic cholangiocarcinoma/unknown	51
Patient 2	59/M	Infections and infestations/sepsis	Intrahepatic cholangiocarcinoma/poorly differentiated	67
Patient 3	39/F	Gastrointestinal disorders/intestinal obstruction	Intrahepatic cholangiocarcinoma/well differentiated	22
Patient 4	63/M	Respiratory, thoracic, and mediastinal disorders/pulmonary embolism	Intrahepatic cholangiocarcinoma/poorly differentiated	76
Ivosidenib after crossover				
Patient 5	70/M	Hepatobiliary disorders/hepatic cirrhosis	Intrahepatic cholangiocarcinoma/moderately differentiated	179
Patient 6	53/F	Gastrointestinal disorders/intestinal pseudo-obstruction	Intrahepatic cholangiocarcinoma/unknown	23

TEAE=treatment-emergent adverse event.

Table S8: **EORTC QLQ-C30 and QLQ-BIL21 key subscale score changes from baseline at cycle 2 day 1 from mixed-effect modelling for ivosidenib versus placebo before crossover (in the intention-to-treat population)**

	EORTC QLQ-C30				EORTC QLQ-BIL21			
	Least square mean change (SE)		Difference, ivosidenib *vs* placebo (95% CI)	p value	Least square mean change (SE)		Difference, ivosidenib *vs* placebo (95% CI)	p value
Subscale	**Ivosidenib (n=62)**	**Placebo (n=20)**			**Ivosidenib (n=60)**	**Placebo (n=19)**		
Physical Functioning (higher scores represent better functioning)	–3·4 (1·8)	–13·1 (3·0)	9·8 (2·8, 16·7)	0·006				
Pain (higher scores represent worse symptoms)	2·7 (2·4)	11·0 (4·1)	–8·2 (–17·6, 1·1)	0·084	5·7 (2·0)	8·7 (3·6)	–2·9 (–11·0, 5·1)	0·473
Appetite Loss* (higher scores represent worse symptoms)	8·9 (2·8)	1·5 (4·8)	7·4 (–3·4, 18·3)	0·177	4·9 (1·9)	2·6 (3·4)	2·4 (–5·2, 10·0)	0·539

A mixed-effect model with repeated measurements on the change from baseline scale score for each key subscale was applied, with baseline score, treatment, visit, and treatment-by-visit as fixed effects, and patient as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used. Two-sided p values are shown. EORTC QLQ-BIL21= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer Module. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. SE=standard error.

*For EORTC QLQ-BIL21, the Eating subscale was assessed.

Table S9: **EORTC QLQ-C30 physical functioning subscale score changes from baseline at cycle 2 day 1 stratified by patient global assessment of change for physical functioning (in the intention-to-treat population)**

	Worsened physical functioning (n=22)	No change in physical functioning (n=25)	Improved physical functioning (n=32)
EORTC QLQ-C30 Physical Functioning subscale*			
Mean (standard deviation)	–13·6 (16·4)	–1·1 (12·1)	0·2 (17·8)
Standard error of measurement†	9·0	6·6	9·7
95% CI	(–20·9, -6·4)	(–6·1, 3·9)	(–6·2, 6·6)
Median (minimum, maximum)	–13·3 (–53·3, 6·7)	0 (–26·7, 26·7)	0 (–40·0, 40·0)
Missing	1	3	1

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

*Higher functioning score represents better level of functioning and better quality of life.

†The standard error of measurement is the standard deviation of measurement errors. This statistic assesses the precision of the observed scores and is calculated by adjusting the standard deviation by the score's reliability. For this analysis, all reliabilities were set to 0·7.

References

1. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods* 1991; **20**: 2609–31.

2. Morden JP, Lambert PC, Latimer N, Abrams KR, Wailoo AJ. Assessing methods for dealing with treatment switching in randomised controlled trials: a simulation study. *BMC Med Res Methodol* 2011; **11**: 4.

3. Watkins C, Huang X, Latimer N, Tang Y, Wright EJ. Adjusting overall survival for treatment switches: commonly used methods and practical application. *Pharm Stat* 2013; **12**: 348–57.

4. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–76.

5. Friend E, Yadegarfar G, Byrne C, et al; EORTC Quality of Life Group. Development of a questionnaire (EORTC module) to measure quality of life in patients with cholangiocarcinoma and gallbladder cancer, the EORTC QLQ-BIL21. *Br J Cancer* 2011; **104**: 587–92.

6. Guy W. ECDEU assessment manual for psychopharmacology. Rockville, MD, USA: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, 1976.

7. Szende A, Janssen B, Cabases J, eds. Self-reported population health: an international perspective based on EQ-5D. Dordrecht, The Netherlands: Springer, 2014.

8. Fan B, Mellinghoff IK, Wen PY, et al. Clinical pharmacokinetics and pharmacodynamics of ivosidenib, an oral, targeted inhibitor of mutant IDH1, in patients with advanced solid tumors. *Invest New Drugs* 2020; 38:433-44.

Study Sponsor:	Agios Pharmaceuticals, Inc. 88 Sidney Street Cambridge, MA 02139-4169 Phone: 617-649-8600 Fax: 617-649-8618
Responsible Medical Officer:	Susan S. Pandya, M.D. Medical Director Agios Pharmaceuticals, Inc. Office Phone: 617.844.6430 Email: susan.pandya@agios.com
Study Medical Monitor	Lawrence Frankel, MD Medical Director, Pharmacovigilance PPD 929 North Front Street Wilmington, NC 28401 Phone: 910-558-7519 Fax: 919-654-9253 Email: lawrence.frankel@ppdi.com
EudraCT Number	2015-005117-72
Document Version (Date):	Original Protocol, Version 1.0 (08 August 2016) Amendment 1, Version 2.0 (05 October 2016) (Global) Amendment 2, Version 3.0 (07 November 2016) (Global) Amendment 2, Version 3.1 (28 April 2017) (UK only) Amendment 3, Version 4.0 (01 September 2017) (Global) Amendment 4, Version 5.0 (04 April 2018) (Global)

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

AGIOS PROTOCOL APPROVAL

I hereby approve this clinical study protocol on behalf of Agios Pharmaceuticals, Inc. (Agios) and attest that it complies with all applicable regulations and guidelines.

Approved by:

Susan Pandya M.D.		05APR2018
Name and Title (Printed)	Signature	Date (DD MMM YYYY)

INVESTIGATOR'S AGREEMENT

I understand that all documentation provided to me by Agios Pharmaceuticals, Inc. (Agios) or its designated representative(s) concerning this study that has not been published previously will be kept in strict confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of Agios and the IRB/IEC, except where necessary to eliminate an immediate hazard to the subject.

I have read, understood, and agree to conduct this study as outlined in the protocol and in accordance with the guidelines and all applicable government regulations.

Investigator Name (printed)	Investigator Signature	Date

Investigational site or name of institution and location (printed)

SYNOPSIS

Name of Sponsor/Company: Agios Pharmaceuticals, Inc.
Name of Investigational Product: AG-120
Name of Active Ingredient: AG-120
Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of AG-120 in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation
Study Center(s): Approximately 55 study centers globally will participate in this study.
Phase of Development: 3

Primary Objective:

- To demonstrate the efficacy of AG-120 based on progression-free survival (PFS) per Independent Radiology Center (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an isocitrate dehydrogenase 1 (IDH1) mutation.

Secondary Objectives:

- To evaluate the safety and tolerability of AG-120 compared to placebo.
- To evaluate PFS per Investigator assessment.
- To compare the efficacy of AG-120 with placebo based on overall survival (OS), objective response rate (ORR), duration of response (DOR), and time to response (TTR), with response assessed per the Investigator and by the IRC.
- To evaluate health-related quality of life (HRQOL) with AG-120 compared to placebo as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ-C30 and EORTC-QLQ-BIL21), the Patient Global Impression of Change (PGI-C), and the Patient Global Impression of Severity (PGI-S).
- To evaluate health economic outcomes as assessed by the 5-level EuroQol five dimensions questionnaire (EQ-5D-5L).
- To evaluate the pharmacokinetics (PK) of AG-120.
- To evaluate the PK/pharmacodynamic (PD) relationship of AG-120 and 2-hydroxyglutarate (2-HG) in blood samples. **Exploratory Objectives:**
- To evaluate, for the subgroup of placebo subjects who have crossed over to the AG-120 arm, the time from first dose of AG-120 to second documented progression on AG-120 or death, whichever occurs first (PFS2).
- To correlate baseline molecular and/or protein characteristics in tumor tissues with clinical response.
- To correlate baseline 2-HG levels in plasma samples with clinical response.

- To evaluate levels of mutant IDH1 and other genes in circulating tumor DNA obtained from plasma at baseline and over the course of the treatment.
- To correlate any PK variations with drug-metabolizing enzyme (DME) related genes, if the data are warranted.
- To explore additional biomarkers in blood for morphologic, functional, biologic, epigenetic, and metabolic changes over the course of treatment.

Methodology:

Study AG120-C-005 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of orally administered AG-120. Subjects, all personnel involved in the evaluation of subjects' response to treatment (eg, Investigators, study coordinators, study pharmacists), and designated Sponsor team members will be blinded to study treatment until documented disease progression. Subjects are required to have a histologically-confirmed diagnosis of IDH1 gene-mutated cholangiocarcinoma that is not eligible for curative resection, transplantation, or ablative therapies. Subjects must have progression of disease and have received at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). All subjects must have received either a gemcitabine or a 5-fluorouracil (5-FU) based chemotherapy regimen.

An independent data monitoring committee (IDMC) will review the safety data on a regular basis to ensure the safety of treatment and proper conduct of the study. The first interim safety review meeting will be conducted when approximately 20 subjects have completed 2 cycles of therapy or have discontinued earlier; thereafter, meetings will be conducted approximately every 3-6 months or on an ad hoc basis. No formal interim analysis for efficacy will be conducted before the primary analysis.

Each subject's course of treatment will be comprised of the following periods:

Pre-Screening Period (Optional): A banked tumor sample (the most recent one available, preferably collected within the last 3 years) or fresh tumor biopsy is required for confirmation of IDH1 gene mutation status by central laboratory testing as part of the subject's eligibility for enrollment (R132C/L/G/H/S mutation variants tested). Potential subjects will sign a pre-screening consent for the purpose of determining IDH1 mutant status. (Potential subjects who do not provide a sample at prescreening will provide one at Screening.)

Pre-Treatment/Screening Period: Following informed consent, all subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on Cycle 1, Day 1 (C1D1), with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. If a tumor sample is not collected during the pre-screening period, a banked or fresh biopsy at Screening will be collected. Additional Screening procedures include medical, surgical, and medication history, radiographic evaluation to determine extent of disease (computed tomography [CT] or magnetic resonance imaging [MRI]), complete physical examination (including height/weight), vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG), echocardiography (ECHO) (or by other methods according to institutional practice) for left ventricular ejection fraction (LVEF) (according to institutional standard of care), a buccal swab for germ-line mutation and DME related gene polymorphism analysis, plasma sample for circulating tumor DNA, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and serum pregnancy test), and blood samples for exploratory biomarker measurement.

Treatment Period and End of Treatment Visit: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive AG-120 orally at a dose of 500 mg once daily (QD) or AG-120-matched oral placebo QD. Randomization will be stratified by number of prior systemic therapies (1 vs 2). Daily study treatment will begin on C1D1. Cycles are 28 days (+/-2 days) in duration and dosing is continuous. All subjects will continue to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. Study visits will be

conducted every other week during Cycles 1-3 (Days 1 and 15), and Day 1 of each cycle thereafter. An End of Treatment (EOT) Visit will be performed on the last day of study treatment (within 5 to 33 days of last dose, to accommodate for potential dosing delays of up to 28 days).

Radiographic assessment (CT or MRI) for evaluation of disease response will be conducted every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48) and every 8 weeks (±5 days) thereafter from C1D1, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. For subjects who discontinue study drug/placebo for reasons other than disease progression or start of another anticancer agent, an assessment will be conducted at the EOT Visit. Upon request by the Investigator, the subject and site staff will be unblinded to treatment assignment after documented disease progression (as assessed by the Investigator and after consultation with the Sponsor Medical Monitor), and subjects randomized to the placebo arm who continue to meet eligibility criteria determined in the EOT visit will be given the opportunity to cross over to the active treatment arm and receive AG-120. For those subjects who cross over, placebo will not be counted as a prior line of therapy for the purpose of eligibility. If subjects cross over, they will start again with study procedures as at C1D1. These subjects will continue to be evaluated for tumor response by the Investigator. If the treatment assignment is determined to be AG-120 upon radiographic disease progression, the Investigator may consider continuing treatment with AG-120, provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression (see Section 9.8 for parameters for treating beyond progression). Palliative radiotherapy to treat symptomatic non-target lesions that cannot otherwise be medically managed will be permitted after disease progression has been verified and unblinding has occurred, with Medical Monitor approval (see Section 9.8.1.3). Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be performed by the institutional radiologist(s). An independent central review of response will be conducted by an Independent Radiology Center (IRC) per RECIST v1.1. All scans will be sent to the IRC as detailed in the site-specific Imaging Core Manual (see Section 10.7.2).

HRQOL assessments will be conducted pre-dose on C1D1 and on Day 1 of every cycle thereafter until the end of treatment. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment will also be conducted at the safety follow-up visit. Health economic outcomes assessments will occur pre-dose on C1D1 Cycle 3, Day 1 (C3D1), and at the EOT Visit. Compliance assessments will occur at Cycle 1, Day 15 (C1D15), Day 1 of every cycle thereafter, and at the EOT Visit. If subjects cross over, they will follow the same assessment schedule as from C1D1.

Subjects will be assessed at every visit for adverse events (AEs) and concomitant medications, starting from the first dose of study treatment. Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Additional safety assessments conducted periodically throughout the study will include vital signs, physical examinations, ECOG PS, ECHO (or other methods according to institutional practice) for determination of LVEF (only if clinically indicated), ECGs, and clinical laboratory assessments (hematology, serum chemistry, and urine pregnancy test).

Blood samples for PK/PD assessments will be drawn over a 4-hour period on C1D1 and C2D1. Additional blood samples for PK/PD assessments will be drawn at 2 hours (±10 minutes) post-dose on C1D15, pre-dose (within 30 minutes) on C3D1 and Day 1 of every cycle thereafter, and at any time during the EOT Visit.

Blood and plasma samples will be obtained for exploratory biomarkers and correlative studies at Screening, C1D15 (plasma only), Day 1 of every cycle thereafter, and at the EOT Visit.

Subjects may continue with their assigned study treatment until disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, until the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first. For subjects who are

determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, Principal Investigators (PIs), with consult from the Sponsor, may keep the subjects on AG-120 after the disease progression.

Post-Treatment Follow-up Visit: A Post-Treatment Follow-Up Visit for safety will occur 28 days (no more than 33 days) after the last dose of study drug. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn. If a subject's dose is interrupted for 28 days and then the subject discontinues study participation, the EOT Visit will serve as the Post-Treatment Follow-up Visit.

PFS and Survival Follow-up: Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent will be followed in PFS follow-up (every 6 weeks through week 48 and every 8 weeks thereafter) until documented disease progression or the initiation of new cancer therapy. If a subject begins a new anticancer therapy during PFS follow-up, information on the new anticancer therapy will be collected.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject progresses or does not come back for scans while in PFS follow-up, then the OS follow-up assessments will begin at the next planned OS follow-up time point, following the schedule of every 12 weeks after EOT. OS follow-up will continue until all subjects have died, withdrawn consent, are lost to follow-up, or until the occurrence of 150 OS events, whichever occurs first.

Number of Subjects (Planned):

A total of approximately 186 subjects will be randomized in a 2:1 ratio, stratified by number of prior systemic treatment regimens for advanced disease (1 or 2) into the 2 treatment arms, including approximately 124 subjects in the AG-120 arm and 62 subjects in the placebo arm.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Subjects must meet all of the following criteria to be enrolled in the study:

1. Be ≥18 years of age.
2. Have a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies.
3. Have documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested).
4. Have an ECOG PS score of 0 or 1 (Appendix 15.1).
5. Have an expected survival of ≥3 months.
6. Have at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or within the field and has shown ≥20% growth in size since post-treatment assessment.
7. Have documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic) with progression on the treatment that was most recently given at a minimum. Subjects must have received at least 1 gemcitabine- or 5-FU-containing regimen for advanced cholangiocarcinoma. Systemic

adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 6 months of completing the therapy.

8. Have recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.
9. Have adequate bone marrow function as evidenced by:
    a. Absolute neutrophil count ≥1,500/mm^3 or 1.5 ×10^9/L
    b. Hemoglobin ≥8 g/dL
    c. Platelets ≥100,000/mm^3 or 100 × 10^9/L
10. Have adequate hepatic function as evidenced by:
    Serum total bilirubin ≤2
    a. Gilbert's disease × upper limit of normal (ULN), unless considered due to
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN 11.

    Have adequate renal function as evidenced by:

    a. Serum creatinine <1.5 × ULN

        OR

    b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR) estimation:

        (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine
12. Be able to understand and willing to sign the informed consent form and to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's IRB/Independent Ethics Committee (IEC). (Subjects who do not speak one of the languages that the EORTC-QLQ-C30, EORTC-QLQ-BIL21, PGI-C, PGI-S, or EQ-5D-5L, are provided in at this time will be permitted to enroll and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria are met.).)
13. Female subjects with reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal (ie, who have not menstruated) for at least 24 consecutive months (ie, have not had menses at any time in the preceding 24 consecutive months). Women with reproductive potential, as well as fertile men and their partners who are female with reproductive potential, must agree to use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug. Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

Exclusion criteria:

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Received a prior IDH inhibitor.
2. Received systemic anticancer therapy or an investigational agent <2 weeks prior to Day 1 (washout from prior immune based anticancer therapy is 4 weeks). In addition, the first dose

of study treatment should not occur before a period ≥5 half-lives of the investigational agent has elapsed.

3. Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.
4. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to Day 1.
5. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and have radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent will be allowed.
6. Have a history of another primary cancer, with the exception of: a) curatively resected nonmelanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor with no known active disease present that, in the opinion of the Investigator, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
7. Underwent major surgery within 4 weeks of Day 1 or have not recovered from post-surgery toxicities.
8. Are pregnant or breastfeeding.
9. Are taking known strong cytochrome P450 (CYP) 3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix 15.2), unless they can be transferred to other medications within ≥5 half-lives prior to dosing.
10. Exclusion criterion 10 removed in Protocol Amendment 4, Version 5.0.
11. Have an active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1 (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
12. Have any known hypersensitivity to any of the components of AG-120 or the matched placebo.
13. Have significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure (Appendix 15.3); myocardial infarction; unstable angina; and/or stroke.
14. Have LVEF <40% by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.
15. Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (Appendix 15.4) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval are permitted with approval of the Medical Monitor.
16. Are taking medications that are known to prolong the QT interval (Appendix 15.5), unless they can be transferred to other medications within ≥5 half-lives prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored.)
17. Have known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted.

18. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
19. Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).
20. Have been committed to an institution by virtue of an order issued either by the judicial or administrative authorities.
21. Are dependent on the Sponsor, Investigator, or study site, per local institution regulations.

Investigational Product, Dosage, and Mode of Administration:

AG-120 will be provided as 250 mg strength tablets to be administered orally.

Subjects randomized to AG-120 will receive 500 mg QD on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing is continuous; there are no planned inter-cycle rest periods.

Duration of Treatment:

Subjects may continue with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, until the subject withdraws consent, is lost to follow-up, or the Sponsor ends the study, whichever occurs first. For subjects who are determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, PIs, with consult from the Sponsor, may keep the subjects on AG-120 after the disease progression.

End of Study:

End of study is defined as the time at which all subjects have died, withdrawn consent, been lost to follow-up, or until the occurrence of 150 OS events. Final analysis for OS will be conducted at the end of the study.

Reference Therapy, Dosage, and Mode of Administration:

Subjects randomized to placebo will receive AG-120-matched placebo tablets to be administered orally on the same schedule as AG-120.

Criteria for Evaluation:

Efficacy:

Serial radiographic evaluations (CT or MRI) to determine response to treatment based on RECIST v1.1. All scans will be sent to the IRC, as detailed in the site-specific Imaging Core Manual (see Section 10.7.2). The EORTC-QLQ-C30, EORTC-QLQ-BIL21, PGI-C, and PGI-S will assess HRQOL and the EQ-5D-5L will assess health economic outcomes.

Safety:

Monitoring of AEs, including serious AEs (SAEs), and AEs leading to discontinuation; safety laboratory parameters; physical examination findings; vital signs; 12-lead ECGs; LVEF; and ECOG PS.

The severity of AEs will be assessed by the NCI CTCAE version 4.03.

Pharmacokinetics and pharmacodynamics:

Serial or sparse blood sampling for determination of pharmacokinetic profiles of AG-120 and inhibition of 2-HG.

Statistical methods:

The primary objective of the study is to demonstrate improvement in PFS by IRC assessment for subjects receiving treatment with AG-120 compared to subjects receiving placebo. Assuming a hazard ratio (HR) of 0.5 for PFS (equivalent to a median PFS of 3 months in the placebo arm versus 6 months in the AG-120 arm, assuming an exponential distribution), a total of 131 PFS events are required to provide 96% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis (see Section 12.7.1) using a stratified log-rank test. Based on this, a total of approximately 186 subjects will need to be randomized in a 2:1 ratio to the AG-120 and placebo arms, respectively, assuming approximately a 22% dropout rate, an approximate 26-month randomization period, and an additional 6-month follow-up for PFS after the last subject is randomized.

Progression-free survival is defined as the time from the date of randomization to the date of first documentation of disease progression or death due to any cause, whichever occurs first. Subjects without documentation of disease progression or death at the time of the primary analysis of PFS will be censored at the date of the last response assessment prior to the start of alternate therapy. Detailed censoring rules will be specified in the Statistical Analysis Plan (SAP). The primary analysis of PFS will be based on IRC response assessments. PFS based on response assessment determined by the Investigator will also be analyzed. Time from first dose of study drug to second documented disease progression (or death) will be calculated for subjects who cross over from the placebo arm to the AG-120 arm (PFS2).

Kaplan-Meier estimates of PFS will be presented for each treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates). The HR of PFS with 95% confidence interval (CI) comparing AG-120 with placebo will be estimated from a Cox proportional hazards model. The log-rank test will be used to compare PFS between the 2 treatment arms.

Overall survival is a secondary endpoint of the study. Subjects will be followed for survival until all subjects have either died, withdrawn consent, are lost to follow-up, or until the occurrence of 150 OS events, whichever occurs first. Kaplan-Meier analysis of OS will be presented. Sensitivity analyses for OS, such as taking into account the factor of cross over, will be specified in the SAP.

Assuming an HR of 0.67 for OS (median OS of 8 months in the placebo arm vs. 12 months in the AG-120 arm, assuming an exponential distribution), a total of 150 OS events will provide 64% power at a 1-sided alpha of 0.025. With a sample size of 186, additional OS follow-up of approximately 24 months after last subject is randomized will be needed to obtain 150 OS events.

ORR, DOR, and TTR are also secondary endpoints and will be analyzed by the IRC and by the Investigator.

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by evaluation of vital signs, ECOG PS, clinical laboratory test results, ECGs, and LVEF data (as clinically indicated). All data will be provided in by-subject listings.

The study data will be analyzed and reported in the primary clinical study report (CSR) based on all subjects' data up to the time when 131 PFS events have been determined by Investigator assessment. Any additional data for survival follow-up and for subjects continuing to receive study treatment past the data cutoff date for the CSR until the occurrence of 150 OS events will be reported at the end of the study in the final CSR.

TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-HG	2-hydroxyglutarate
5-FU	5-flurouracil
α-KG	Alpha-ketoglutarate
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myelogenous leukemia
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0\text{-}12hr}$	Area under the concentration × time curve from 0 to 12 hours
BCRP	Breast cancer resistance protein
BID	Twice daily
BUN	Blood urea nitrogen
CxDx	Cycle x, Day x
CI	Confidence interval
CIMP	Cytosine-guanine dinucleotide island methylator phenotype
C_{max}	Maximum concentration
CpG	Cytosine-guanine dinucleotide
CO_2	Carbon dioxide
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity

DME	Drug-metabolizing enzyme
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram

Abbreviation	**Definition**
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC-QLQ-BIL21	European Organisation for Research and Treatment of Cancer - Quality Of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality Of Life Questionnaire – Core Questionnaire
EOT	End of treatment
EQ-5D-5L	5-level EuroQol five dimensions questionnaire
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GLP	Good Laboratory Practice
HBV, HCV	Hepatitis (B/C) virus
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQOL	Health-related quality of life
ICH	International Council for Harmonisation
IDH, IDH1, IDH2	Isocitrate dehydrogenase protein, 1, 2
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Radiology Center
ITT	Intent-to-Treat

IWRS	Interactive web response system
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mSv	Millisievert
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association

Abbreviation	**Definition**
ORR	Objective response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Pharmacodynamic
PFS	Progression-free survival
PFS2	Time from first dose to second objective disease progression or death
PGI-C	Patient Global Impression of Change (PGI-C)
PGI-S	Patient Global Impression of Severity (PGI-S)
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial response
PS	Performance status
QD	Once daily
QTcB, QTcF	Heart-rate corrected QT interval (using Bazett's / Fridericia's formula)
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set

SD	Stable disease
$t_{½}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of normal

INTRODUCTION

3.1. *Cellular Metabolism and Cancer*

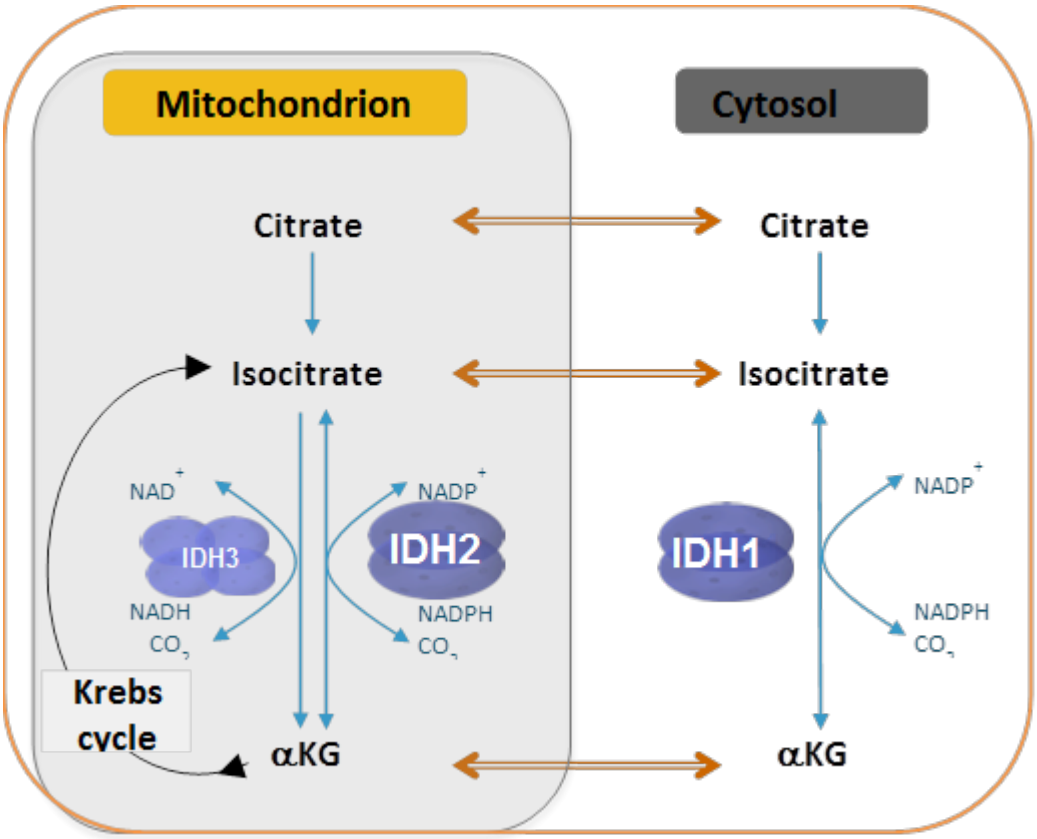
3.1.1. *The Role of Isocitrate Dehydrogenase*

The isocitrate dehydrogenase (IDH) proteins are critical metabolic enzymes that exist as 3 isoforms: IDH1, IDH2, and IDH3 (Figure 1). All 3 catalyze the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO_2) and alpha-ketoglutarate (α-KG). IDH1 and IDH2 produce adenine dinucleotide phosphate (NADPH) whereas IDH3 only produces NADH.

Cancer-associated mutations have been identified in IDH1 and IDH2; however to date, no mutations have been described in IDH3 (Yen, et al. 2010). One fundamental difference between IDH1 and IDH2 is the subcellular localization of the 2 proteins. IDH1 is localized in both peroxisomes and cytosol (Geisbrecht and Gould 1999; Yoshihara, et al. 2001). IDH2 is a mitochondrial isoform of IDH (Wang, et al. 2013; Yoshihara, et al. 2001).

The genes encoding IDH1 and IDH2 are located on chromosome 2q33.3 and 15q26.1, respectively. Mutations in these IDH proteins most commonly lead to alterations affecting arginine-132 (R132H or R132C) in IDH1, and the analogous arginine residue (arginine-172 mutated to lysine [R172K]) or arginine-140 (R140Q) in IDH2.

Figure 1: The Citric Acid Cycle



3.1.2. *Tumorigenesis Hypothesis*

Mutant IDH1 and IDH2 are not catalytically inactive enzymes, but rather possess novel enzymatic activities, consistent with a gain-of-function, reconciling the heterozygous nature of the point mutations (Dang, et al. 2009). The mutated proteins themselves have a

gain-of-function, neomorphic activity, catalyzing the reduction of α-KG to 2-hydroxyglutarate (2-HG) (Dang, et al. 2009). The Sponsor's studies established that purified mutant protein efficiently catalyzes the proposed reduction of α-KG to 2-HG, while being unable to synthesize isocitrate (Dang, et al. 2009). Mutations in IDH1 and IDH2 are almost always mutually exclusive and occur at very early stages of tumor development suggesting that they promote formation and progression of tumors (Welch, et al. 2012).

Evidence supports that cancer-associated IDH mutations block normal cellular differentiation and promote tumorigenesis via the abnormal production of 2-HG, a potential oncometabolite. High levels of 2-HG have been shown to inhibit α−KG dependent dioxygenases including histone and deoxyribonucleotide demethylases, which play a key role in regulating the epigenetic state of cells (Chowdhury, et al. 2011; Koivunen, et al. 2012; Xu, et al. 2011). Consistent with 2-HG promoting tumorigenesis via an effect on chromatin structure, patients with IDH mutations display a cytosine-guanine dinucleotide (CpG) island methylator phenotype (CIMP) and several studies have shown that overexpression of IDH mutant enzymes can induce histone and deoxyribonucleic acid (DNA) hypermethylation as well as impair normal cellular differentiation (Figueroa, et al. 2010; Lu, et al. 2012; Turcan, et al. 2012).

Clinical studies in several tumor types including glioma and acute myelogenous leukemia (AML) have found elevated levels of 2-HG in cells with mutant IDH1 and IDH2 as compared to cells with wild-type alleles (Gross, et al. 2010; Ward, et al. 2010). In normal cells, 2-HG is present in low levels. However, IDH1/IDH2 mutations in cancer cells result in the excess accumulation of 2-HG to extremely high levels, which can alter a number of downstream cellular activities. The elevated levels of 2-HG also are present in the sera and urine of some affected patients. Efforts are underway in the ongoing Phase 1 study (AG120-C-002) to explore the association of plasma and tissue 2-HG with underlying tumor burden and tumor response in cholangiocarcinoma and other solid tumors.

3.1.3. *IDH Mutations in Cholangiocarcinoma and Other Solid Tumors*

IDH1 mutations continue to be identified in a variety of solid tumor subtypes, including gliomas, chondrosarcomas, and intrahepatic cholangiocarcinomas. Mutations in IDH1 have been found in approximately 70% of Grade 2 to 3 gliomas (Yan, et al. 2009), 50% of chondrosarcomas (Amary, et al. 2011), and 20% of intrahepatic cholangiocarcinomas (Borger, et al. 2012) and a smaller percentage of extra-hepatic cholangiocarcinomas (Kipp, et al. 2012).

IDH1 mutations are relevant therapeutic targets in cholangiocarcinoma as they may play a role in the pathogenesis of the disease by blocking the differentiation of liver progenitor cells and promoting cellular proliferation (Saha, et al. 2014). The majority of available data suggest IDH1 mutations are not associated with prognosis in cholangiocarcinoma unlike IDH1 mutations in glioma, which are associated with improved outcomes (Goyal, et al. 2015).

3.2. *Overview of Cholangiocarcinoma*

Based on the available incidence data, which combines intrahepatic cholangiocarcinoma with cancers arising in the hepatocytes, approximately 6000 patients with cholangiocarcinoma (15% of 39,230) are diagnosed each year in the US (AJCC 2010; Siegel, et al. 2016). The expected incidence of cholangiocarcinoma in the European Union (EU) is 0.84/100,000 (RARECARE 2016).

The management of this disease includes multi-modality treatment: biliary decompression, surgery, radiation and other interventions for local disease control, liver transplantation, and chemotherapy. In the advanced, nonresectable setting, the disease is incurable and palliative chemotherapy is the primary treatment option. Monotherapy and combination chemotherapy approaches with gemcitabine- or 5-flourouracil-based regimens are often considered in this setting. In the ABC-02 trial, a study in patients with advanced biliary cancers including cholangiocarcinoma, the combination of gemcitabine and cisplatin improved progression-free survival (PFS) (hazard ratio [HR]: 0.63, 8.0 vs. 5.0 months, P<0.001) and overall survival (HR:
0.64, 11.7 vs. 8.1 months, P<0.001) compared to gemcitabine alone (Valle, et al. 2010). Thus the combination of gemcitabine and cisplatin is a standard option in the first-line setting for patients with advanced nonresectable disease.

Second-line chemotherapy regimens produce an incrementally smaller benefit with an average median PFS of 2 to 3 months (Brieau, et al. 2015; Lamarca, et al. 2014). However, despite current treatment options, prognosis for this population remains poor with 5-year survival rates ranging from 2% to 30% (ACS 2014).

Given the overall poor outcomes associated with consecutive chemotherapy regimens in patients with cholangiocarcinoma, there is an urgent need for the development of novel targeted therapies for patients with this serious and life-threatening disease.

3.3. *AG-120*

3.3.1. *Overview*

AG-120 is a potent and selective inhibitor of the IDH1 mutant protein with no significant offtarget activity observed. The compound has been demonstrated to reduce 2-HG levels by >95%, to reverse growth factor-independent growth *in vitro*, and to induce differentiation in leukemia cell models. Preliminary clinical data in patients with advanced hematologic malignancies harboring an IDH1 mutation (AG120-C-001) and with advanced solid tumors harboring an IDH1 mutation (AG120-C-002) have shown the compound to be well tolerated at total daily doses up to 1200 mg with clinical activity observed in both solid and liquid tumors. The 500 mg dose level of AG-120 was expanded and selected for future studies based on the available pharmacokinetic (PK)/pharmacodynamic (PD), safety profile, and preliminary clinical activity observed.

3.3.2. *Summary of Nonclinical Information*

Details of the nonclinical development program for AG-120 are provided in the Investigator's Brochure. A summary of the key information is provided below.

3.3.2.1. Pharmacokinetic Drug Interactions

AG-120 is mainly metabolized by CYP3A4, with minor contributions from CYP2B6 and CYP2C8. Therefore, co-administration with CYP3A4 inhibitors or inducers could have an effect on the PK of AG-120.

AG-120 is an inducer of human CYP3A4 and may also be an inducer of CYP2B6, CYP2C8, and CYP2C9. Therefore, there is a possibility of PK drug-drug interactions when AG-120 is coadministered with sensitive substrates of CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5. AG-120 is a weak direct inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 with IC_{50} values >50 µM and shows little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9. AG-120 shows no time- or metabolism-dependent inhibition of any of the CYP enzymes evaluated. The likelihood of inhibition of CYP enzymes by AG-120 is, therefore, extremely low.

AG-120 is a substrate of P-glycoprotein (P-gp) but not breast cancer resistance protein (BCRP). However, coadministration of itraconazole (a strong P-gp inhibitor) had no effect on the maximum concentration (C_{max}) of AG-120 in human subjects, suggesting the involvement of intestinal P-gp in AG-120 disposition in vivo is likely to be minimal. AG-120 is not a substrate of OATP1B1 or OATP1B3 transporters.

AG-120 does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, and OCT2 at clinically relevant concentrations. AG-120 appears to be a weak inhibitor of OATP1B1 and OATP1B3, with IC_{50} values of 9.56 and 22.8 µM, respectively. AG-120 does not inhibit the OAT1- and OCT2-mediated uptake of the probe substrate (IC_{50} > 65 µM) but inhibits OAT3 (IC_{50} ~0.322 µM).

3.3.2.2. Safety Pharmacology and Toxicology

The toxicity profile of AG-120 has been evaluated *in vitro* in the bacterial reverse mutation assay and *in vivo* in Sprague Dawley rats and cynomolgus monkeys. The compound was not mutagenic and was well tolerated at estimated efficacious exposures with a potential 4-fold therapeutic window.

Safety pharmacology

Individual animals with possible (≥30 msec) and probable (≥60 msec) test article-related QT prolongation corrected for heart rate using Bazett's formula (QTcB) (Morganroth 2001) have been noted in both the 28-day and 3-month Good Laboratory Practice (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.

Toxicology

In GLP 28-day repeat-dose toxicology studies, oral doses of AG-120 administered twice daily (BID) at the projected human efficacious exposure were well tolerated by both rats and monkeys. In rats, significant findings at 100 mg/kg/day were limited to minimal alterations in clinical pathology parameters, liver and thyroid findings consistent with autoinduction of metabolism, and splenic extramedullary hematopoiesis. In monkeys, significant findings at 30 mg/kg/day were limited to gastrointestinal clinical observations and sporadic emesis. In both species, all significant effects at projected efficacious exposures were reversible over the 14-day recovery period.

In the GLP 28-day rat study, dose-limiting toxicity (DLT) occurred at a dosage of 2000 mg/kg/day. At this dose level, significantly reduced exposures were observed, from 15-fold the projected efficacious exposure on Day 0 to 5.4- to 7.8-fold on Day 27, which were consistent with autoinduction of metabolism. The majority of the unscheduled deaths occurred early in the study, between Days 2 and 6, suggesting that these early mortalities were being driven by the higher exposures. The cause of this early DLT was multifactorial and included moderate, bridging, centrilobular hepatocellular degeneration and necrosis with additional contributing factors being tubular necrosis in the kidney; cortical and medullary tubular vacuolation in the kidney; atrophy of small intestines; hypocellularity, hemorrhage and necrosis of the femoral and/or sternal bone marrow; and erosions of the glandular stomach. When DLT occurred later in the dosing period (the minority of the early mortality), it was due to mucosal atrophy of the intestines, erosions and ulcerations of the glandular stomach and/or rectum, and lymphoid depletion and necrosis in lymphoid organs with renal tubular necrosis being an additional contributing factor. Exposures at this time were likely closer to the Day 27 exposures. The Day 27 AG-120 area under the concentration × time curve from 0 to 12 hours ($AUC_{0\text{-}12hr}$) value for this dosage was 69500 and 101000 hr•ng/mL, in males and females, respectively, which is 1.2- and 1.8-fold the human $AUC_{0\text{-}10hr}$, respectively.

The next lower dose level tested in rats (500 mg/kg/day) resulted in an $AUC_{0\text{-}12hr}$ values of 30100 and 59000 hr•ng/mL in males and females, respectively, which is 0.5- and 1-fold the human $AUC_{0\text{-}10}$. No early mortality occurred and this exposure level was tolerated. All significant findings at this dose level were reversible.

In the GLP 3-month rat study, AG-120 was well tolerated at dosage levels of 20, 100, and 500 mg/kg/day in rats and resulted in no test article-related deaths. Test article-related effects were qualitatively similar at 100 and 500 mg/kg/day. Most findings had resolved during the 4-week recovery period. At 500 mg/kg/day, the Day 90 mean plasma $AUC_{0\text{-}12hr}$ values were 29000 and 62000 ng•hr/mL in males and females, respectively (0.5- and 1.1-fold the human $AUC_{0\text{-}10hr}$ value), and at 100 mg/kg/day were 12100 and 20000, respectively (0.2- and 0.3-fold the human $AUC_{0\text{-}10hr}$ value). At 500 mg/kg/day, the Day 90 mean plasma C_{max} values were 4650 and 9710 ng/mL in males and females, respectively, and at 100 mg/kg/day were 2770 and 5660 ng/mL, respectively. The Day 90 mean plasma $AUC_{0\text{-}12hr}$ values at 20 mg/kg/day were 6880 and 7090 ng•hr/mL in males and females, respectively (0.1-fold the human $AUC_{0\text{-}10hr}$ value), and the Day 90 mean plasma C_{max} values were 1320 and 1580 ng/mL, respectively. The findings observed in the 3-month rat study are largely consistent with those noted at tolerable doses in the 28-day study with the exception of the novel finding of a higher potassium fractional urine excretion.

In the GLP 28-day monkey study, DLT occurred in male monkeys at an $AUC_{0\text{-}12hr}$ value of 235000 (at a dose of 270 mg/kg/day), which is 4.1-fold the human $AUC_{0\text{-}10hr}$ value. The cause of DLT was general malaise characterized by poor body condition and gastrointestinal clinical signs leading to emesis and secondary aspiration. In females at the same dose level, AG-120 was tolerated and the Day 27 $AUC_{0\text{-}12hr}$ value was 109000 hr•ng/mL, which is 1.9-fold the human $AUC_{0\text{-}10hr}$ value. The dosage of 270 mg/kg/day was associated with significant weight loss and moribundity; higher total, direct, and indirect bilirubin and triglycerides; lower hemoglobin and hematocrit values; lower phosphorous levels; lower albumin and total protein; higher mean specific gravity and lower total urine volume; ventricular bigeminy; prolonged QTcB in females; higher liver weights; and hepatocellular hypertrophy. All significant findings were reversible following the recovery period, with the exception of the cardiovascular findings, for which recovery was not assessed because the affected animals were assigned to the primary necropsy. In the GLP 3-month monkey study, AG-120 at dosage levels of 30, 90, and 180 mg/kg/day for up to 92 consecutive days was well tolerated at all dosage levels and resulted in no test article-related deaths. Test article-related effects included diarrhea in males at ≥30 mg/kg/day and females at 180 mg/kg/day, and hepatocellular hypertrophy and higher liver weights at ≥30 mg/kg/day. Likely test article-related prolongations of QTcB were noted in individual animals in the 90 and 180 mg/kg/day dose groups at free C_{max} exposure margins ≥1.3-fold that of the human 500 mg C_{max} value. All test article-related changes resolved during the recovery period. The 180 mg/kg/day dose level was associated with gender combined Day 90 mean plasma C_{max} and $AUC_{0\text{-}12hr}$ values of 14800 ng/mL and 134000 ng•hr/mL, respectively (2.3-fold the human $AUC_{0\text{-}10hr}$ value). The findings observed in the 3-month monkey study are largely consistent with those noted at tolerable doses in the 28-day study.

3.3.3. *Summary of Clinical Data*

The AG-120 clinical development program was initiated in March 2014 with 2 Phase 1 dose escalation studies, AG120-C-001 and AG120-C-002. Refer to the Investigator's Brochure for further details on each of these studies.

3.3.3.1. Study AG120-C-002

Study AG120-C-002 is evaluating the safety, PK, PD biomarker patterns, and clinical activity of AG-120 in subjects with advanced solid tumors, including cholangiocarcinoma, with an IDH1 mutation. The primary objectives of the study are to assess the safety and tolerability of treatment with AG-120 administered daily as a single agent dosed orally in subjects with advanced solid tumors, including glioma, and to determine the maximum tolerated dose(s) (MTD[s]) and/or the recommended Phase 2 dose(s) of AG-120 in this population. The initial dosing regimen was 100 mg BID and doses up to 1200 mg once daily (QD) were assessed in a 3+3 dose escalation design; based on the favorable PK profile showing a long elimination halflife ($t_{½}$), BID dosing was discontinued after the first cohort and a QD dosing regimen was implemented. The study is divided into a dose escalation phase, followed by an expansion phase to allow for a more robust evaluation of the safety profile and preliminary assessment of clinical activity. This study is currently ongoing.

As of 16 January 2016, 122 subjects with solid tumors have been treated in Study AG120-C-002; 69 of the 122 subjects remain on treatment. Thirty-seven of the subjects in Study AG120-C-002 have a primary malignancy of cholangiocarcinoma.

Treatment with AG-120 has been well tolerated; no DLTs have been reported. Overall, 101 (83%) of 122 subjects have reported treatment-emergent adverse events (TEAEs). To date, the most commonly reported adverse events (AEs) have been nausea (20%), fatigue (12%), diarrhea, (11%), prolonged QT interval (10%), and vomiting (10%). There was no evidence for an increase in the incidence of these commonly reported events with dose.

Two deaths within 30 days of study treatment termination have been reported in the 400 mg dose cohort. One was due to anemia and the other occurred due to acute respiratory failure. Both deaths were assessed as unrelated to study treatment.

A total of 20 (16%) of the 122 subjects have experienced serious AEs (SAEs). No individual SAE was reported in more than 1 subject, and none of these SAEs were assessed to be related to AG-120. The only SAE experienced by more than one subject was headache (2 subjects, 2%); additional SAEs were reported in 1 subject each. Only an event of supraventricular extrasystoles was assessed as possibly related to study treatment.

Preliminary analysis of PK data at the 100 mg BID and, 300, 400, 500, 600, 800, 900, and 1200 mg QD dose levels demonstrated excellent oral AG-120 exposure that on Cycle 1, Day 15 (C1D15) and Cycle 2, Day 1 (C2D1) was above the predicted efficacious exposure of 12.9 hr•µg/mL that was associated with 97% tumor 2-HG inhibition (direct IDH1 pathway inhibition PD biomarker) in nonclinical models; mean $t_{½}$ was from 38.4 to 86.2 hours, which enables a QD oral dosing schedule.

Evaluation of 2-HG as a direct inhibition of the IDH1 pathway PD biomarker response following AG-120 dosing in the 100 mg BID and 300, 400, 500, 600, 800, 900, and 1200 mg QD dose cohorts demonstrated sustained reduction in 2-HG plasma levels (up to 100% inhibition) by C2D1 at all dose levels.

As of 14 April 2016, 48 subjects with cholangiocarcinoma have been treated, including 24 subjects in the dose escalation phase and 24 in the expansion phase. At the time of the data cutoff, 23 of the 48 subjects remain on treatment and 25 have discontinued (19 due to disease progression and 2 each due to AE, withdrawal of consent, and other reasons). The overall safety profile of AG-120 remains consistent with that reported in the most recent Investigator's Brochure. Of the 48 cholangiocarcinoma subjects, 38 were evaluable for the analysis of efficacy (ie, had a baseline tumor measurement and at least 1 post-baseline response assessment or discontinued earlier). Three subjects (8%) with cholangiocarcinoma receiving AG-120 (1 at 300 mg and 2 at 500 mg) had an objective partial response, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 15.9). In addition, 22 subjects (58%) had stable disease (SD), 11 subjects (29%) experienced disease progression as best response. Two subjects (8%) were not assessed for response (discontinued treatment prior to a response assessment). At the 6-month time point, 60% of subjects were progression free (PFS6) as assessed by the Kaplan-Meier method. As of the data cutoff, three subjects remained on study drug >1 year with an overall best response of SD.

There were no dose limiting toxicities. Based on the available pharmacokinetic data (suggesting less than dose proportional increase in exposure beyond 500 mg and maximal plasma 2-HG suppression at 500 mg) and following review of data from the dose escalation phase of this study, AG-120 500 mg QD was determined to be a safe and potentially effective dose for further study.

3.3.3.2. Study AG120-C-001

Study AG120-C-001 is evaluating the safety, PK, PD biomarker patterns, and clinical activity of AG-120 in subjects with advanced AML and related hematologic malignancies that harbor an IDH1 mutation. The primary objectives of the study are to assess the safety and tolerability of treatment with AG-120 administered daily in subjects with advanced hematologic malignancies, to determine the MTD and/or the recommended Phase 2 dose of AG-120 in this population, and to assess the preliminary clinical activity of AG-120 in subjects with relapsed or refractory AML with an IDH1 mutation. The initial dosing regimen was BID; based on the favorable PK profile showing a long $t_{½}$, BID dosing was discontinued after the first cohort and a QD dosing regimen was implemented. Like the AG120-C-002 study, this study is divided into a dose escalation phase, followed by an expansion phase to allow for a more robust evaluation of the safety profile and preliminary assessment of clinical activity. This study is currently ongoing. A summary of the data from this study is provided in the Investigator's Brochure for AG-120.

3.4. *Identified Risks of AG-120*

Clinical safety data for AG-120 are described in Section 5.3.3. The only expected risk of treatment with AG-120 in patients with solid tumors, as detailed in the Investigator's Brochure, is prolonged QT interval. Patients may be at increased risk for development of QT prolongation when treated with AG-120 in combination with

fluoroquinolones, azole antifungal agents, or serotonin (5-HT_3) antagonists. Investigators need to be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor patients receiving AG-120 with the combination of these drugs, and evaluate electrocardiogram (ECG) and electrolytes (including potassium, magnesium, and calcium) particularly in patients presenting with nausea, vomiting, or diarrhea. For more information, see Section 9.9.

Refer to the AG-120 Investigator's Brochure for the full details regarding the risks of AG-120 therapy.

3.5. *Study Rationale*

AG-120 is a novel, first-in-class compound targeted selectively to inhibit the mutated IDH1 enzyme. Small molecule inhibition of the mutant IDH enzyme represents a novel, targeted approach to cancer treatment. Direct inhibition of the gain-of-function activity of the IDH1 mutated protein is intended to inhibit the production of the oncogenic metabolite 2-HG. AG-120 has been extensively evaluated in nonclinical studies and has been shown *in vitro* and *in vivo* to effectively inhibit the gain-of-function activity of the mutated protein leading to >95% inhibition of the production of the potential oncometabolite 2-HG. In clinical studies, up to 98% inhibition of plasma 2-HG has been observed in subjects with solid tumors after QD dosing of AG-120. The preliminary Phase 1 clinical data (from 14 April 2016) with AG-120 in the population of subjects with previously treated IDH1 mutant cholangiocarcinoma have shown the compound to be well tolerated with evidence of clinically meaningful activity including partial responses (RECIST v1.1) and durable disease control with 60% of subjects progression free at 6 months (PFS6). Based on the supportive efficacy and safety data (see Section 5.3.3.1), AG-120 may serve as a novel molecularly targeted treatment option for patients with previously treated IDH1 mutated cholangiocarcinoma.

Study AG120-C-005 is a randomized, double-blind, placebo-controlled study designed to demonstrate the efficacy and safety of AG-120 in subjects with a histologically-confirmed diagnosis of IDH1 gene-mutated cholangiocarcinoma compared to placebo. Patients eligible for the study are those who have disease progression following at least 1 but no more than 2 prior treatment regimens in the advanced setting, including 1 gemcitabine or 5-flurouracil (5-FU)containing regimen, and who are not eligible for curative resection, transplantation, or ablative therapies.

There are no standard treatment options for patients who have progressed on a gemcitabine- or 5FU-based chemotherapy regimen and palliative care is oftentimes instituted, thus a placebo control is acceptable. The study allows for subjects in the placebo arm to cross over to the AG-120 arm upon documented disease progression as long as they meet eligibility criteria determined in the EOT Visit. Cross over subjects will follow the same assessment schedule as from C1D1.

TRIAL OBJECTIVES AND ENDPOINTS

4.1. *Primary Objective*

The primary objective of the study is:

- To demonstrate the efficacy of AG-120 based on PFS per Independent Radiology Center (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

4.2. *Secondary Objectives*

The secondary objectives of the study are:

- To evaluate the safety and tolerability of AG-120 compared to placebo.
- To evaluate PFS per Investigator assessment.
- To compare the efficacy of AG-120 with placebo based on overall survival (OS), objective response rate (ORR), duration of response (DOR), and time to response (TTR), with response assessed per Investigator and by the IRC.
- To evaluate health-related quality of life (HRQOL) with AG-120 compared to placebo as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC-QLQ-C30 and EORTC-QLQBIL21), the Patient Global Impression of Change (PGI-C), and the Patient Global Impression of Severity (PGI-S).
- To evaluate health economic outcomes as assessed by the 5-level EuroQol five dimensions questionnaire (EQ-5D-5L).
- To evaluate the PK of AG-120.
- To evaluate the PK/PD relationship of AG-120 and 2-HG in blood samples.

4.3. *Exploratory Objectives*

The exploratory objectives of the study are:

- To evaluate, for the subgroup of placebo subjects who have crossed over to the AG-120 arm, the time from first dose of AG-120 to second documented progression on AG-120 or death, whichever occurs first (PFS2).
- To correlate baseline molecular and/or protein characteristics in tumor tissues with clinical response.
- To correlate baseline 2-HG levels in plasma samples with clinical response.
- To evaluate levels of mutant IDH1 and other genes in circulating tumor DNA obtained from plasma at baseline and over the course of the treatment.
- To correlate any PK variations with drug-metabolizing enzyme (DME) related genes, if the data are warranted.
- To explore additional biomarkers in blood for morphologic, functional, biologic, epigenetic, and metabolic changes over the course of treatment.

4.4. *Study Endpoints*

4.4.1. *Primary Endpoint*

- The primary endpoint is PFS, defined as the time from date of randomization to date of first documented disease progression (as assessed by the IRC per RECIST v1.1), or date of death due to any cause.

4.4.2. *Secondary Endpoints*

- AEs, SAEs, AEs leading to discontinuation or death. The severity of AEs will be assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
- Safety laboratory parameters, vital signs, 12-lead ECGs, evaluation of left ventricular ejection fraction (LVEF), Eastern Cooperative Oncology Group (ECOG) performance status (PS), and concomitant medications.
- Secondary efficacy endpoints include:
  - OS, defined as the time from date of randomization to date of death.
  - ORR, defined as the proportion of subjects with a best overall response defined as CR or PR, as assessed by the Investigator and by the IRC per RECIST v1.1.
  - DOR, defined as the time from date of first documented complete response (CR) or partial response (PR) to date of first documented disease progression or death due to any cause, as assessed by the Investigator and by the IRC per RECIST v1.1.
  - TTR, defined as the time from date of randomization to date of first documented CR or PR for responders, as assessed by the Investigator and by the IRC per RECIST v1.1.
  - PFS as determined by the Investigator.
- HRQOL as assessed by validated instruments (EORTC-QLQ-C30, EORTC-QLQBIL21, PGI-C, and PGI-S) (EORTC 1995; Friend, et al. 2011).
- Health economic outcomes as assessed by the EQ-5D-5L instrument (Szende 2014).
- Serial or sparse blood sampling at specified time points for determination of plasma concentration-time profiles and PK parameters of AG-120.
- Blood sampling at specified time points for determination of 2-HG levels to characterize the PD effects of AG-120.

4.4.3. *Exploratory Endpoints*

- Baseline molecular and protein profiling using banked or fresh tumor samples.
- Evaluation of mutant IDH1 levels and other genes in circulating tumor DNA using serial plasma samples.
- Serial blood and/or plasma samples for morphologic, functional, epigenetic, biologic, and metabolic profiling.
- Correlation of germline DNA drug metabolism, clearance related gene polymorphisms with PK variance, safety, and/or efficacy using buccal swab germline DNA samples, if the data are warranted.

INVESTIGATIONAL PLAN

5.1. *Overall Study Design*

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of orally administered AG-120 in subjects with advanced cholangiocarcinoma (nonresectable or metastatic). Subjects, all personnel involved in the evaluation of subjects' response to treatment (eg, Investigators, study coordinators, study pharmacists), and designated Sponsor team members will be blinded to study treatment until documented disease progression. Subjects are required to have a histologically consistent diagnosis of IDH1 gene-mutated cholangiocarcinoma that is not eligible for curative resection, transplantation, or ablative therapies. Subjects must have documented progression of disease and have received treatment with at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). At least 1 of the prior regimens must have included gemcitabine or 5-FU. Systemic adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 6 months of completing the therapy, with Sponsor approval. A total of approximately 186 subjects will be randomized in a 2:1 ratio to the AG-120 and placebo arms, respectively, stratified by number of prior therapies (1 vs. 2). The enrollment duration will be approximately 26 months, assuming an initial 5 subjects per month enrollment rate for the first 6 months and 8 subjects per month thereafter. The primary analysis of PFS will occur once 131 PFS events have been determined by Investigator assessment (approximately 6 months after the last subject is randomized). OS will be analyzed twice, once at the time of PFS primary analysis and once at the occurrence of 150 OS events (approximately 24 months after the last subject is randomized).

An independent data monitoring committee (IDMC) will review the safety data on a regular basis to ensure the safety of treatment and proper conduct of the study. The first interim safety review meeting will be conducted when approximately 20 subjects have completed 2 cycles of therapy or have discontinued earlier; thereafter, meetings will be conducted every 3-6 months or on an ad hoc basis. No formal interim analysis for efficacy will be conducted before the primary analysis.

Each subject's course of treatment will be comprised of the following periods:

Pre-Screening Period (Optional): A banked tumor sample (the most recent one available, preferably collected within the last 3 years) or fresh tumor biopsy is required for confirmation of IDH1 gene mutation status by central laboratory testing, as part of the subject's eligibility for enrollment (R132C/L/G/H/S mutation variants tested). Potential subjects will sign a pre-screening consent for the purpose of determining IDH1 mutant status. (Potential subjects who do not provide a sample at pre-screening will provide one at Screening.)

Pre-Treatment/Screening Period: Following informed consent, all subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on Cycle 1, Day 1 (C1D1), with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. If a tumor sample is not collected during the prescreening period, a banked or fresh biopsy at Screening will be collected. Additional Screening procedures include review of entry criteria, recording of demographics and disease history, medical, surgical, and medication history, radiographic evaluation to determine extent of disease (computed tomography [CT] or magnetic resonance imaging [MRI]), complete physical examination (including height/weight), vital signs, ECOG PS, 12-lead ECG, echocardiography (ECHO) (or other methods according to institutional practice) for LVEF (according to institutional standard of care), a buccal swab for germ-line mutation and DME related gene polymorphism analysis, plasma sample for circulating tumor DNA, clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, and serum pregnancy test), and blood samples for exploratory biomarker measurement.

Treatment Period and End of Treatment Visit: Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio to receive AG-120 orally at a dose of 500 mg QD or AG-120-matched oral placebo QD. Randomization will be stratified by number of prior systemic therapies (1 vs 2). Daily study treatment will begin on C1D1. Cycles are 28 days (+/-2 days) in duration and dosing is continuous. All subjects will continue to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. Study visits will be conducted every other week during Cycles 1-3 (Days 1 and 15), and Day 1 of each cycle thereafter. An End of Treatment (EOT) Visit will be performed on the last day of study treatment (within 5 to 33 days of last dose, to accommodate for potential dosing delays of up to 28 days). Radiographic assessment (CT or MRI) for evaluation of disease response will be conducted every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48) and every 8 weeks (±5 days) thereafter from C1D1, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. For subjects who discontinue study drug/placebo for reasons other

than disease progression or start of another anticancer agent, an assessment will be conducted at the EOT Visit. Upon request by the Investigator, the subjects and site staff will be unblinded to treatment assignment after documented disease progression (as assessed by the Investigator) in consultation with the Sponsor Medical Monitor, and subjects randomized to the placebo arm who continue to meet eligibility criteria determined in the EOT visit will be given the opportunity to cross over to the active treatment arm and receive AG-120. For those subjects who cross over, placebo will not be counted as a prior line of therapy for the purpose of eligibility. If subjects cross over, they will start again with study procedures as at C1D1. These subjects will continue to be evaluated for tumor response by the Investigator. If the treatment assignment is determined to be AG-120 upon radiographic disease progression, the Investigator may consider continuing treatment with AG-120, provided the subject is clinically benefitting and there is no contraindication to continuing treatment beyond progression (see Section 9.8 for parameters for treating beyond progression). Target and non-target lesion selection and objective tumor response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be performed by the institutional radiologist(s). An independent central review of response will be conducted by an Independent Radiology Center (IRC) per RECIST v1.1. All scans will be sent to the IRC as detailed in the site-specific Imaging Core Manual (see Section 10.7.2).

HRQOL assessments will be conducted pre-dose on C1D1 and on Day 1 of every cycle thereafter until EOT. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment will also be conducted at the safety follow-up visit. Health economic outcomes assessments will occur pre-dose on C1D1, C3D1, and at the EOT Visit. Compliance assessments will occur at C1D15, Day 1 of every cycle thereafter, and at the EOT Visit. If subjects cross over, they will follow the same assessment schedule as from C1D1.

Subjects will be assessed at every visit for AEs and concomitant medications, starting from the first dose of study treatment. Toxicity severity will be graded according to the NCI CTCAE version 4.03. Hematology and serum chemistry will be assessed on Days 1 and 15 of Cycles 1-3, on Day 1 of each treatment cycle thereafter, and at the EOT Visit. Limited physical examinations and vital signs assessments will be performed on Day 1 of each cycle, with a complete physical examination and vital signs conducted at the EOT Visit; vital signs will also be assessed on C1D15 and C2D15. Urinalysis and coagulation testing will only be performed at Screening.
ECOG PS will be assessed on C1D1, Day 1 of each treatment cycle thereafter, and at the EOT Visit. ECGs will be obtained pre-dose on C1D1 and C2D1, 2 hours post-dose on C1D1, C1D15, and C2D1, anytime on Day 1 of subsequent cycles, and at the EOT Visit. Echocardiography (or other methods according to institutional practice) to assess LVEF will be performed (according to institutional standard of care) only if clinically indicated.

Blood samples for PK/PD assessments will be drawn over a 4-hour period on C1D1 and C2D1. Additional blood samples for PK/PD assessments will be drawn at 2 hours (±10 minutes) post dose on C1D15, pre-dose (within 30 minutes) on C3D1 and Day 1 of each treatment cycle thereafter, and at any time during the EOT Visit.

Blood and plasma samples will be obtained for exploratory biomarkers and correlative studies at Screening, C1D15 (plasma only), Day 1 of every cycle thereafter, and at the EOT Visit. Subjects may continue with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first. For subjects who are determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, Principal Investigators (PIs), with consult from the Sponsor, may keep the subjects on AG-120 after the disease progression.

Post-Treatment Follow-up Visit: A Post-Treatment Follow-Up Visit for safety will occur 28 days (no more than 33 days) after the last dose of study drug. Every effort must be made to perform protocol-specified evaluations unless consent to participate in the study is withdrawn. Assessments to be performed at the Follow-up Visit include ECOG PS and AE and concomitant medication recording. If a subject's dose is interrupted for 28 days and then the subject discontinues study participation, the EOT Visit will serve as the Post-Treatment Follow-up Visit. **PFS and Survival Follow-up:** Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent will be followed in PFS follow-up (every 6 weeks through week 48, and every 8 weeks thereafter) until documented disease progression or the initiation of new cancer therapy. If a subjects begins a new anticancer therapy during PFS follow-up, information on the new anticancer therapy will be collected.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject progresses or does not come back for scans while in PFS follow-up, then the OS follow-up assessments will begin at the next planned OS follow-up time point, following the schedule of every 12 weeks

after EOT. OS follow-up will continue until all subjects have died, withdrawn consent, are lost to follow-up, or until the occurrence of 150 OS events, whichever occurs first.

End of Study: End of study is defined as the point in time when all subjects have died, withdrawn consent, been lost to follow-up, or until 150 OS events have occurred. Final analysis for OS will be conducted at the end of the study.

5.2. *Justification of the Study Design*

The study is designed as a randomized, double-blind, placebo-controlled efficacy and safety study. Subjects will be randomly assigned in a 2:1 ratio to receive AG-120 or AG-120-matched placebo. Random assignment of subjects avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. The study includes a matched placebo arm with blinding of all site personnel involved in the evaluation of subjects' response to treatment (eg, Investigators, study coordinators, study pharmacists); this design allows for control of potential influences of the natural course of the disease other than those related to the pharmacologic action of the test drug, and reduces bias in subjective assessments, including both efficacy and safety evaluations. Eligible subjects will continue to receive best supportive care throughout the duration of the study.

An IDMC will review safety data at scheduled intervals as outlined in Section 10.5.1.

Demonstration of the efficacy of AG-120 as assessed by PFS is the primary objective of the study. Response assessments used to determine PFS will be based on standard response criteria (RECIST v1.1) with the primary endpoint based on IRC response assessments.

Secondary endpoints include safety, OS, ORR, DOR, TTR, HRQOL, and health economic outcomes. PFS per Investigator assessment is also a secondary endpoint. Analyses of ORR, DOR, and TTR based on response assessments will be performed as determined by the IRC and by the Investigator.

5.3. *Rationale for the Dose Selected*

Preliminary data have shown AG-120 to be well tolerated at total daily doses up to 1200 mg in solid tumors (AG120-C-002) and in hematologic malignancies (AG120-C-001); the MTD was not reached in either study. As of a 16 January 2016, 122 subjects have been treated with AG-120 in the AG120-C-002 study, of which 84 subjects received 500 mg QD; 119 subjects have been treated with AG-120 in the AG120-C-001 study, of which 89 subjects received 500 mg QD. Based on a review of the available safety, PK/PD, and clinical activity data observed during dose escalation, 500 mg QD was selected as the AG-120 dose for the expansion phases of both of these trials.

In these studies, there have been minimal dose interruptions, and without an apparent dose relationship for any commonly reported TEAEs or Grade ≥3 TEAEs. No DLTs have been reported in Study AG120-C-002. Dose-limiting toxicities of Grade 3 rash and Grade 3 QT prolongation were observed in the 1200 mg QD and 800 mg QD cohorts respectively in Study AG120-C-001; however, expansion of these dose cohorts did not result in identification of the MTD.

Plasma AG-120 exposure increased in a less than proportional manner across doses from 100 mg BID to 1200 mg QD, nearing a plateau at 500 mg QD, in both solid tumors and hematologic malignancies. Sustained and consistent plasma 2-HG inhibition was observed with plasma 2-HG levels reduced to the normal range of healthy volunteers (up to 98.0% inhibition in solid tumors,

99.7% in hematologic malignancies) at all doses, with no apparent dose response. The 500 mg QD dose has shown a maximum PD effect based on 2-HG levels for the majority of subjects. As of 14 April 2016, AG-120 was associated with clinical activity in subjects with cholangiocarcinoma, including 3 subjects with best overall response of PR and 22 subjects with best overall response of stable disease in the dose escalation and expansion phases of AG120-C002. Of the 48 subjects with cholangiocarcinoma (both dose escalation and expansion phases) in Study AG120-C-002, 37 subjects received 500 mg QD doses of AG-120.

5.4. *Criteria for Study Termination*

This study may be prematurely terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. In the event of such action, written notification documenting the reason for study termination will be provided to each Investigator.

The study will be terminated if any of the following circumstances occur:

- Determination of unexpected, significant, or unacceptable risk to subjects. (An IDMC will review the safety data on a regular basis to ensure the risk/benefit ratio.)
- Failure to enter subjects at an acceptable rate.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue the development of the study treatment.
- Other administrative reasons.

If the study is terminated early for any reason other than unacceptable toxicity, Sponsor will continue to provide drug to subjects who are benefiting from treatment. Should the study be closed prematurely due to unacceptable toxicity, all study materials must be returned to the Sponsor or Sponsor's designee.

STUDY POPULATION

6.1. *Number of Subjects*

A total of approximately 186 subjects will be randomized in a 2:1 ratio, stratified by number of prior systemic treatment regimens for advanced disease (1 or 2) into the 2 treatment arms, including approximately 124 subjects in the AG-120 arm and 62 subjects in the placebo arm.

6.2. *Inclusion Criteria*

Subjects must meet all of the following criteria to be enrolled in the study:

1. Be ≥18 years of age.
2. Have a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies.
3. Have documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested).
4. Have an ECOG PS score of 0 or 1 (Appendix 15.1).
5. Have an expected survival of ≥3 months.
6. Have at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or within the field and has shown ≥20% growth in size since post-treatment assessment.
7. Have documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic). Subjects must have received at least 1 gemcitabine- or 5-FU-containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy will be considered a line of treatment if there is documented disease progression during or within 6 months of completing the therapy.
8. Have recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.
9. Have adequate bone marrow function as evidenced by:
    a. Absolute neutrophil count ≥1,500/mm^3 or 1.5 ×10^9/L
    b. Hemoglobin ≥8 g/dL
    c. Platelets ≥100,000/mm^3 or 100 × 10^9/L
10. Have adequate hepatic function as evidenced by:
    a. Serum total bilirubin ≤2 × upper limit of normal (ULN), unless considered due to Gilbert's disease

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN

11. Have adequate renal function as evidenced by:
    a. Serum creatinine <1.5 × ULN

       OR

    b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR) estimation:

       (140 − Age) × (weight in kg) × (0.85 if female)/72 × serum creatinine

12. Be able to understand and willing to sign the informed consent form and to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC). (Subjects who do not speak one of the languages that the QLQ-C30, QLQ-BIL21, PGI-C, PGI-S, or EQ-5D-5L are provided in at this time will be permitted to enroll and not complete these HRQOL/health economic outcome instruments, assuming all other eligibility criteria are met.)
13. Female subjects with reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal (ie, who have not menstruated) for at least 24 consecutive months (ie, have not had menses at any time in the preceding 24 consecutive months). Women of reproductive potential, as well as fertile men and their partners who are female with reproductive potential, must agree to use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug. Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

6.3. *Exclusion Criteria*

Subjects who meet any of the following criteria will not be enrolled in the study:

1. Received a prior IDH inhibitor.
2. Received systemic anticancer therapy or investigational agent <2 weeks prior to Day 1 (washout from prior immune based anticancer therapy is 4 weeks). In addition, the first dose of study treatment should not occur before a period ≥5 half-lives of the investigational agent has elapsed.
3. Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.
4. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to Day 1.
5. Have known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and have radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent will be allowed.
6. Have a history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumor with no known active disease present that, in the opinion of the Investigator, will not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.
7. Underwent major surgery within 4 weeks of Day 1 or have not recovered from postsurgery toxicities.
8. Are pregnant or breastfeeding.
9. Are taking known strong CYP3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix 15.2), unless they can be transferred to other medications within ≥5 half-lives prior to dosing.

10. Exclusion criterion 10 removed in Protocol Amendment 4, Version 5.0.
11. Have an active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1 (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
12. Have any known hypersensitivity to any of the components of AG-120 or the matched placebo.
13. Have significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure (Appendix 15.3); myocardial infarction; unstable angina; and/or stroke. 14. Have LVEF <40% by ECHO scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.
15. Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF)

    (Appendix 15.4) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval are permitted with approval of the Medical Monitor.
16. Are taking medications that are known to prolong the QT interval (Appendix 15.5),

    unless they can be transferred to other medications within ≥5 half-lives prior to dosing or unless the medications can be properly monitored during the study. (If equivalent medication is not available, QTcF should be closely monitored.)
17. Have known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS) related illness. Subjects with a sustained viral response to HCV or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted.
18. Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.
19. Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).
20. Have been committed to an institution by virtue of an order issued either by the judicial or administrative authorities.
21. Are dependent on the Sponsor, Investigator, or study site, per local institution regulations.

6.4. *Subject Identification and Registration*

Subjects who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria (see Section 8.2 and Section 8.3, respectively) have been satisfied and that the subject is eligible for participation in this clinical study. The Medical Monitor will confirm eligibility for all subjects prior to randomization.

6.5. *Subject Withdrawal Criteria*

Subjects have the right to withdraw from the study at any time for any reason. A subject's discontinuation of study treatment or withdrawal from the study will not jeopardize the relationship with their healthcare providers or affect their future care. Subjects may choose to discontinue study treatment but agree to remain on study for follow-up contact. This decision must be recorded in writing by the study site.

Should a subject decide to withdraw, all efforts will be made to complete and report the protocol-defined study observations as completely as possible and to determine the reason for withdrawal.

In the event a subject discontinues study treatment or withdraws from the study, the Medical Monitor must be informed. If there is a medical reason for withdrawal, the subject will remain under the supervision of the Investigator until satisfactory health has returned.

When a subject discontinues study treatment or withdraws from the study, the primary reason for discontinuation or withdrawal must be recorded in the appropriate section of the electronic case report form (eCRF) and all efforts will be made to complete and report final study observations as thoroughly as possible.

6.5.1. *Withdrawal from Study Treatment*

Subjects may discontinue or be discontinued from study treatment at any time. In this situation, a subject without documented progressive disease by the Investigator should be followed for tumor assessments until the development of progressive disease and/or survival. Subjects will be discontinued from study treatment for the following reasons:

- Withdrawal of consent
- Certain adverse events (as described in Section 9.8) including instances of Grade 4 QTcF prolongation.
- Disease progression (subjects who are, in the opinion of the Investigator, benefitting from treatment [eg, slow progression] may be allowed to continue on study treatment with approval of the Medical Monitor)
- Death
- Investigator decision
- Subject decision to withdraw from treatment (subject may continue with PFS and/or survival follow-up)
- Protocol violation: non-adherence to study treatment regimen or protocol requirements
- Confirmed pregnancy (study therapy should be immediately interrupted based upon a positive urinary human chorionic gonadotropin [hCG] test, and permanently discontinued if confirmed by a serum β-hCG test)
- Lost to follow-up

All AEs should be followed until resolution or for a period of 28 days from the last dose of study treatment, whichever is shorter. If the subject withdrew from treatment because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures.

6.5.2. *Study Termination*

Subjects who discontinue treatment without disease progression or death will continue to be followed for PFS every 6 weeks after the EOT Visit (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) thereafter until disease progression, death, start of subsequent anticancer therapy, or withdrawal of consent. After subjects have discontinued treatment because of disease progression, they will be contacted approximately every 12 weeks to assess survival status (OS) and to document receipt of subsequent anticancer therapy unless consent to participate is withdrawn. Subjects will be terminated from the study for the following reasons:

- Death
- Withdrawal of consent
- Loss to follow-up
- Occurrence of 150 OS events
- Sponsor termination of the study

If subjects are terminated from the study because of the occurrence of 150 OS events or Sponsor decision, Sponsor will continue to provide drug to subjects who are benefiting from treatment.

STUDY TREATMENT

7.1. *Description of Study Treatment*

AG-120 will be administered orally at a dose of 500 mg (provided as 250 mg strength tablets). Placebo will be supplied as matched tablets to be administered orally.

7.2. *Study Treatment Packaging and Labeling*

AG-120 and matched placebo will be supplied in appropriate containers with child resistant closures and will be labeled appropriately as investigational product for this study. Packaging and labeling will be prepared to meet all regulatory requirements.

7.3. *Study Treatment Storage*

AG-120 tablets and matched placebo tablets must be stored according to the package label.

All study treatment products must be stored in a secure, limited-access location and may be dispensed only by the Investigator or by a member of the staff specifically authorized by the Investigator.

7.4. *Method of Assigning Subjects to Treatment*

Subjects who meet all study eligibility criteria will be randomly assigned in a 2:1 ratio, stratified by number of prior systemic treatment regimens for advanced disease (1 or 2), to receive AG-120 orally QD or AG-120-matched placebo orally QD.

The randomization schedule will be generated by an independent statistical group. The randomization assignment will be implemented by an interactive web response system (IWRS).

7.5. *Blinding*

The subjects, Investigators, the clinical research unit staff who deal directly with subjects, and the Sponsor will be blinded to study treatment assignment until documented disease progression.
The IWRS will assign each subject specific Medication ID-labeled study drug containers. AG120 and placebo will be packaged and labeled identically so that the study pharmacist will remain blinded to treatment assignment.

The subjects, clinical research unit staff, and Sponsor will remain blinded for the duration of the study unless emergency unblinding is required (see Section 9.6). Upon request by the
Investigator, subjects and staff will be unblinded at the time of disease progression as confirmed by study sponsor.

An IDMC will review unblinded safety and other clinical data at scheduled meetings; the unblinded summaries will be prepared by an independent statistical center (Section 10.5.1).

7.6. *Unblinding*

The need to unblind study treatment should first be discussed with the Sponsor's Medical
Monitor (or Responsible Medical Officer), if at all possible. In the event of a medical emergency or pregnancy in a female subject or in the sexual partner of a male subject, in which knowledge of the investigational product is critical to the subject's management, the study treatment may be unblinded for that subject by the treating Investigator. Investigators are encouraged to discuss a plan to break the blinding code with the Medical Monitor.

In case of an emergency, the Investigator may access the IWRS to reveal the identity of the treatment for that subject. Once the decision to unblind has been made, the Investigator must record the nature of the emergency that required the unblinding, along with the date and time of the unblinding on the proper source documentation and notify the Sponsor's Medical Monitor (or Responsible Medical Officer) of the unblinding.

In the event that a subject's treatment assignment is unblinded, either accidentally or in the case of emergency unblinding, the subject will be allowed to continue study treatment. In the case of emergency unblinding, if the subject is receiving placebo, cross over to AG-120 will not be permitted until documented progression.

Upon request by the Investigator, the subject and site staff will be unblinded to treatment assignment after documented disease progression (as assessed by the Investigator and after consultation with the Sponsor Medical Monitor), and subjects randomized to the placebo arm who still meet eligibility criteria will be given the opportunity to cross over to the active treatment arm and receive AG-120. For those subjects who cross over, placebo will not be counted as a prior line of therapy for the purpose of eligibility. If subjects cross over, they will follow the same assessment schedule as from C1D1. These subjects will continue to be evaluated for tumor response by the Investigator. If the treatment assignment is determined to be AG-120 upon radiographic disease progression, the Investigator may consider continuing AG-120, provided the subject appears to be clinically benefitting and there is no contraindication to continuing treatment beyond progression (see Section 9.8 for parameters for treating beyond progression).

Palliative radiotherapy to treat symptomatic non-target lesions per RECIST v1.1 that cannot otherwise be medically managed will be permitted after disease progression has been verified and unblinding has occurred (see Section 9.8.1.3). AG-120 should be held for the duration of palliative radiotherapy. Palliative radiotherapy and any other anti-cancer therapy will not be permitted during the blinded portion of this study. Any decision to pursue palliative radiotherapy will require Medical Monitor approval. After palliative radiotherapy, there will be a 2-week washout period before the start or resumption of AG-120 treatment. For subjects randomized to placebo who receive palliative radiotherapy before crossing over to AG-120, a repeat CT or MRI will be performed at the end of the 2-week washout period, which will serve as the new baseline for comparison for all subsequent scans in order to assess PFS2 (see Section 12.12.1). For subjects permitted to continue on open-label AG-120 beyond documented radiographic progression, a new baseline imaging assessment will not be required and the imaging assessments will continue on the current schedule.

7.7. *Study Treatment Preparation and Administration*

Daily treatment with AG-120 or placebo will begin on C1D1; clinical observations will be conducted over 4 hours following the first dose of study treatment on C1D1. Dosing is continuous; there are no planned inter-cycle rest periods. Subjects should be instructed to take their QD dose at approximately the same time each day.

Subjects should be instructed to swallow tablets whole and to not chew the tablets. Subjects may take AG-120 or placebo tablets with or without food. Subjects should be advised that if AG-120/placebo tablets are taken with food, the subject should avoid grapefruit or grapefruit products and avoid consuming a high-fat meal. Please refer to examples of low-fat and high-fat meals in Appendix 15.6.

If the subject forgets to take the daily dose, then they should take AG-120 or placebo within 12 hours after the missed dose. If more than 12 hours have elapsed, then that dose should be omitted, and the subject should resume treatment with the next scheduled dose.

Subjects will continue to receive best supportive care throughout the study, regardless of treatment arm.

Subjects may continue with their assigned study treatment until disease progression, development of unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first. For subjects who are determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, PIs, with consult from the Sponsor, may keep the subjects on AG-120 after the disease progression.

7.8. *Criteria for Dose Modification, Discontinuation of Study Treatment,* Continuation Beyond Radiographic Progression, and Allowance of Palliative Radiotherapy

7.8.1. *Study Treatment Dose Modification and Stopping Criteria*

7.8.1.1. Dose Modifications and Delays

For any AE, including AEs not specifically mentioned in Table 1, the Investigator may decide to delay dosing or modify the dose of AG-120/placebo based on clinical judgment. These decisions should be discussed with the Medical Monitor prior to implementation. Dose modifications of AG-120/placebo from 500 mg to 250 mg will be permitted on study for management of AEs (Table 1). If more than one AE occurs that would require a dose

modification, upon resolution of all AEs to baseline or Grade 1, AG-120/placebo should be dose reduced to 250 mg. Reescalation may be allowed with approval from the Medical Monitor.

Dose delays are discouraged, except as needed for management of AEs, dose holds during palliative radiotherapy, and washout from palliative radiotherapy. Dose delays up to 28 days will be permitted at the discretion of the Investigator in consultation with the Medical Monitor for reasons including management of AEs and for mitigating circumstances (eg, planned procedures). Palliative radiotherapy delivered in the unblinded open-label cross over period or in the setting of continuation of AG-120 beyond disease progression will require a 2-week washout period after radiotherapy before the resumption of AG-120 treatment (see Section 9.8.1.3). Palliative biliary decompression procedures will be permitted on study and will not require interruption of AG-120/placebo.

If the subject cannot resume AG-120/placebo within 28 days, the subject should be discontinued from study medication. Other reasons for treatment termination are provided in Section 8.5. If AG-120 or placebo is discontinued, the subject will complete the EOT and Follow-up Visits, and then enter PFS follow-up (if disease has not progressed) and survival follow-up. Exemptions may be considered for those subjects who are determined by the Investigator to have received clinical benefit from treatment. If a dose is delayed for the management of an AE, the subject should resume the study at the next planned visit within a dosing cycle (eg, if the subject did not start dosing at C3D1 due to management of an AE, then dosing would be resumed at C3D1 upon resolution of the AE, not C3D15).

Table 1: Management of Adverse Events

Adverse Events	Action
Grade 2 nausea or vomiting (related or unrelated)	• Consider holding dose of AG-120/placebo until resolution of AE to Grade ≤1 within 28 days of supportive therapy. • Manage with supportive therapy according to the institutional standard of care. • May resume AG120/placebo at same dose.
Grade 3 adverse events (related, first event)	• Hold dose of AG-120/placebo until resolution to Grade ≤1 or baseline within 28 days of supportive therapy and then resume dose. • Manage with supportive therapy according to the institutional standard of care. • If the Grade 3 AE recurs (a second time), consider reducing AG120/placebo to 250 mg in consultation with the Medical Monitor. Reescalation may be permitted after discussion with the Medical Monitor. • If the Grade 3 AE recurs (a third time) despite dose reduction of AG120/placebo, then consider discontinuing AG-120/placebo in consultation with the Medical Monitor.
Grade 4 adverse events (related, first event)	• Hold AG-120/placebo. • Manage with supportive therapy according to the institutional standard of care. • If the AE resolves to Grade ≤1 or baseline within 28 days, then restart AG120/placebo dosing at 250 mg in consultation with the Medical Monitor. • If the AE does not resolve to Grade ≤1 or baseline within 28 days, consider discontinuing study treatment in consultation with the Medical Monitor. • If the Grade 4 AE recurs (a second time), despite dose reduction, AG120/placebo should be discontinued in consultation with the Medical Monitor.

*See Table 2 for specific dose modifications for QTcF prolongation.

7.8.1.2. Continuation of Treatment Beyond Radiographic Progression

In the event of radiographic progression per RECIST v1.1 but in the absence of clinical deterioration, worsening ECOG performance status, or disease progression that may compromise organ function, the subject may continue to receive study treatment with AG-120 at the discretion of the treating physician in consultation with the Sponsor Medical Monitor. If there is clinical deterioration or continued radiographic progression documented on subsequent imaging, treatment will be discontinued and the subject will complete the EOT and Follow-up Visits, and enter survival follow-up.

7.8.1.3. Palliative Radiotherapy After Unblinding After Disease Progression

Palliative radiotherapy to treat symptomatic pre-existing or new non-target lesions (per RECIST v1.1) that cannot otherwise be medically managed will be permitted after disease progression has been confirmed and unblinding has occurred. AG-120 should be held for the duration of palliative radiotherapy. A 2-week washout from completion of radiotherapy will be required prior to starting or resuming AG-120. For subjects randomized to placebo who receive palliative radiotherapy before crossing over to AG-120, a repeat CT or MRI will be performed upon completion of the 2-week washout period to document the area that was irradiated and to serve as the new baseline against which all subsequent RECIST v1.1 assessments will be performed, for the purpose of documenting PFS2 during the unblinded open-label cross over period (see Section 12.12.1). For subjects permitted to continue on open-label AG-120 beyond documented radiographic progression, a new baseline imaging assessment will not be required and the imaging assessments will continue on the current schedule. All decisions to pursue palliative radiotherapy will require Medical Monitor approval.

7.8.1.4. Biliary Tract Obstruction During Treatment

In the event of the development of obstructive jaundice due to biliary tract obstruction, the appropriate measures will be taken to diagnose and relieve the obstruction. Study treatment interruption is not required, but will be permitted at the discretion of the Investigator.

7.9. *Guidelines for Management of QT Prolongation*

The discussion of the emergency management of Torsades de pointes and its hemodynamic consequences is beyond the scope of this guideline.

Events of QTcF prolongation ≥Grade 2 should be reported as AEs of special interest (AESIs) to the Sponsor within 24 hours, according to expedited reporting procedures (see Section 11.2.3).

The following are guidelines for the management of AEs of special interest based on the AG-120 non-clinical and clinical safety findings in subjects with solid tumors to date.

Prolongation of QTcF interval has been observed in monkeys at relatively high doses of AG-120 (see Section 5.3.2.2) and has been identified as an expected risk of treatment with AG-120 (see the Investigator's Brochure). As of 16 January 2016, 12 (10%) of 122 subjects in Study AG120-C-002 and 19 (16%) of 119 subjects in Study AG120-C-001 have experienced QT prolongation while receiving AG-120.

Subjects may be at increased risk for the development of QT prolongation when treated with AG-120 in combination with fluoroquinolones, azole antifungal agents, or serotonin ($5\text{-}HT_3$) antagonists. Investigators need to be vigilant; refrain from administering concomitant medications associated with QT prolongation and if no other therapeutic options are available, monitor subjects receiving study treatment with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea. Systemic administration of a moderate or strong CYP3A4 inhibitor requires careful monitoring of QTcF (see Section 9.13.2).

Subjects who experience prolongation of the QTcF interval to >480 msec (CTCAE Grade ≥2) while receiving study treatment, should be promptly evaluated for causality of the QTcF prolongation and managed according to the following guidelines and Table 2:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.

- If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator), study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held.
- ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction ≤480 msec.

Table 2: Management of QT Prolongation by CTCAE Grade

CTCAE Grade	Management
Grade 2 (QTcF >480 and ≤500 msec)	• The dose of study treatment may be reduced to 250 mg QD without interruption of dosing. The dose of study treatment may be re-escalated the prior dose in ≥14 to days after QT prolongation has decreased to ≤Grade 1.
Grade 3 (QTcF >500 msec on at least two separate ECGs)	• Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. • Dosing with study treatment will be interrupted. If QTcF returns to within 30 msec of baseline or <450 msec for males and <470 msec for females within 14 days, treatment may be resumed at a reduced dose of 250 mg. • The dose of study treatment cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
Grade 4 (QTcF >500 msec or >60 msec change from baseline with Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Subjects should be admitted to a hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. • Dosing with study treatment should be permanently discontinued.

7.10. *Duration of Subject Participation*

7.10.1. *Treatment Duration*

Treatment with AG-120 or placebo will continue until disease progression, development of other unacceptable toxicity, confirmed pregnancy, death, withdrawal of consent, the subject is lost to follow-up, or the Sponsor ends the study, whichever occurs first. For subjects who are determined to be on AG-120 upon radiographic disease progression and demonstrate clinical benefit, PIs, with consult from the Sponsor, may keep the subjects on AG-120 after the disease progression.

Following discontinuation of study treatment, subjects are to attend a Follow-up Visit at least 28 days and no more than 33 days after the last dose for study assessments. When study treatment is withheld from a subject in order to resolve toxicity and the subject does not subsequently restart treatment, EOT is defined as the date when the study drug was first held. Subjects should proceed with EOT assessments, safety, PFS, and survival follow-up. If the decision to not restart study treatment occurs outside of the 28-day safety follow-up window, the subject should proceed with PFS and survival follow-up.

Subjects will be contacted approximately every 12 weeks after EOT to assess survival status, HRQOL (until the start of new anticancer therapy), and to document receipt of subsequent anticancer therapy unless consent to participate is withdrawn.

7.11. *Treatment Compliance*

Subjects will be dispensed the appropriate number of Sponsor-packaged, labeled bottle(s) for at least 28 days of dosing on Day 1 of each cycle. The subject will be asked to return all bottles and unused tablets (or empty bottles) on Day 1 of each cycle or at their next study visit for assessment of compliance with the dosing regimen.

Subjects will be given a Sponsor- and IRB-approved dosing diary for each treatment cycle. They should record relevant information regarding their study treatment in the diary (eg, confirmation that each daily dose was taken, reasons for missed doses). Treatment compliance will be assessed based on return of unused drug and the dosing diary.

7.12. *Study Treatment Accountability*

Accountability for the study treatment at the study site is the responsibility of the Investigator. The Investigator will ensure that the study treatment is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual.

The Investigator or delegate will maintain accurate drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to the Sponsor or its designee (or disposal of the drug, if approved by the Sponsor). These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study treatment received from the Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

Study treatment must not be used for any purpose other than the present study. Study treatment that has been dispensed to a subject and returned unused must not be re-dispensed to a different subject.

Subjects will receive instructions for home administration of study treatment along with a diary to record the date and time of each dose, as well as the number of tablets taken.

All unused and used study treatment should be retained at the site until they are inventoried and verified by study site personnel and/or the study monitor. All used, unused, or expired study treatment will be returned to the Sponsor or its designee or if authorized, disposed of at the study site per the site's Standard Operating Procedures (SOPs) and documented. All material containing AG-120 and/or matched placebo will be treated and disposed of as hazardous waste in accordance with governing regulations.

7.13. *Prior and Concomitant Medications and Treatments*

7.13.1. *Prior Medications and Procedures*

All medications administered and procedures conducted within 28 days prior to the first day of study treatment administration are to be recorded on the eCRF. In addition, all prior treatments for the underlying malignancy should be recorded.

7.13.2. *Concomitant Therapy Requiring Careful Monitoring*

Concomitant use of drugs with a potential QT prolongation should be avoided and replaced with alternative treatments. If this is not possible, subjects receiving these drugs should be adequately monitored.

These medications include but are not limited to:

- Fluoroquinolones such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (5-HT_3) antagonists such as granisetron and ondansetron

Other examples of drugs known to prolong the QT interval are listed in Appendix 15.5.

Systemic administration of moderate or strong CYP3A4 inhibitors (Appendix 15.6) requires careful monitoring of the QTc (see Section 9.13.4).

7.13.3. *Prohibited Concomitant Therapy*

Anticancer therapy other than the treatment outlined in the protocol is not permitted during the study. If alternative therapy is required for treatment of the subject's disease, the subject should be discontinued from the study treatment.

7.13.4. *Drug-Drug Interactions*

AG-120 is mainly metabolized by CYP3A4 and, therefore, subjects should not use strong CYP3A4 inducers (Appendix 15.2) during treatment with AG-120.

AG-120 clinical trials and physiologically based pharmacokinetic (PBPK) simulations have shown that AG-120 plasma concentrations increase with co-administration of a strong or moderate CYP3A4 inhibitor, and increased AG-120 plasma concentrations may increase the risk of QTc prolongation. Therefore, alternative therapies that are not strong or moderate CYP3A4 inhibitors should be considered during treatment with AG-120. If concomitant use of strong or moderate CYP3A4 inhibitors is unavoidable, subjects should be monitored for increased risk of QTc prolongation.

AG-120 is an inducer of human CYP3A4/5 and may also induce CYP2B6, CYP2C8, and CYP2C9. Therefore, medications of sensitive CYP3A4 substrates with a narrow therapeutic window (Appendix 15.2) should be avoided unless the subject can be transferred to other medications prior to enrolling. Consider alternative therapies that are not sensitive substrates of CYP2C9 (eg, phenytoin, warfarin). Monitor international normalized ratio (INR) levels more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of AG-120.

AG-120 is an inhibitor of OAT3. A PBPK simulation predicted an increase (<30%) in the AUC of a sensitive OAT3 substrate, suggesting that the potential for clinically relevant drug interactions due to the inhibition of OAT3 appears to be low.

Coadministration of AG-120 may decrease the concentrations of hormonal contraceptives.

7.13.5. *Allowed Concomitant Medications, Procedures, and Treatments*

Medications and treatments other than those specified above are permitted during the study. All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the Investigator according to acceptable local standards of medical care.

If clinically indicated, palliative biliary decompression procedures will be permitted on-study after discussion with the Medical Monitor.

Subjects should receive analgesics, antiemetics, anti-infectives, antipyretics, blood products, and any other best supportive care measures (excluding anticancer therapy) as necessary, assuming no drug interaction potential.

Palliative radiotherapy for symptomatic non-target lesions that cannot otherwise be medically managed will be permitted after Medical Monitor approval after disease progression has been verified and unblinding has occurred, and in the setting of continuation of AG-120 beyond disease progression, as described in Section 9.8.1.3.

Growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) can be used to support subjects who have developed doselimiting Grade 4 neutropenia or Grade 3 neutropenia with fever and/or infection. The use of erythropoiesis stimulating agents is permitted according to the American Society of Clinical Oncology Guidelines (Rizzo, et al. 2010).

All concomitant medications and any procedures performed during the study, including those used to treat AEs, are to be reported on the eCRF.

STUDY ASSESSMENTS

8.1. *Schedule of Events*

Table 3 provides the schedule of assessments for this study. Pre-screening or screening for IDH1m will occur at a central lab using either the most recent banked tumor sample (preferably from within the last 3 years) or a fresh biopsy. Potential subjects will sign a pre-screening or screening consent form for the purpose of determining IDH1

mutant status (R132C/L/G/H/S mutation variants tested). After obtaining written informed consent for the study overall, all subjects will undergo Screening procedures to determine eligibility within 28 days prior to the start of study treatment on C1D1, with the exception of baseline radiographic scans, which should be performed within 21 days prior to C1D1. Subjects are to attend study center visits as outlined in the Schedule of Assessments (Table 3).

Study center visits will be conducted on an outpatient basis whenever possible. Subjects are to remain at the study center for 4 hours following the C1D1 and C2D1 doses for PK/PD and ECG assessments (Table 4). After the Screening Visit, a symptom-directed, limited physical exam should be performed at each Cycle, Day 1 visit, per institution standards of care.

An EOT Visit will be conducted as soon as possible after discontinuing study treatment (within 5 days of last dose of study treatment, if study drug dosing has not been delayed); in addition, subjects are to attend a Follow-up Visit 28 days (no more than 33 days) after the last dose of study treatment for final safety assessments. If a subject's dose is held and it is subsequently decided to discontinue treatment, the EOT Visit should be conducted as soon as possible, within 28 days (and no more than 33 days) after the last dose of study drug.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject progresses or does not come back for scans while in PFS follow-up, then the OS follow-up assessments will begin at the next planned OS follow-up time point, following the schedule of every 12 weeks after EOT. OS follow-up will assess survival status and documentation of receipt and type of subsequent anticancer therapy unless consent to participate is withdrawn. If a subject begins a new anticancer therapy during PFS follow-up, information on the new therapy will need to be entered. OS follow-up will continue until all subjects have died, withdrawn consent, are lost to follow-up, or until the occurrence of 150 OS events, whichever occurs first. HRQOL (until the start of new anticancer therapy) assessments will be collected every 12 weeks after EOT.

Subjects who cross over from the placebo arm to the active arm after documented disease progression, must continue to meet eligibility criteria determined in the EOT visit and will start again with study procedures as at C1D1. For those subjects who cross over, placebo will not be counted as a prior line of therapy for the purpose of eligibility. These subjects will continue to be evaluated for tumor response by the Investigator. For subjects who receive palliative radiotherapy after unblinding and during the cross over period, there will be a 2-week washout period after radiotherapy before the start of AG-120 treatment (see Section 9.8.1.3). A repeat CT or MRI will be performed at the end of the 2-week washout period to document the area that was irradiated and to serve as the new baseline against which all subsequent RECIST v1.1 assessments will be performed, for the purpose of documenting PFS2 during the unblinded openlabel cross over period (see Section 12.12.1).

Palliative radiotherapy delivered in the setting of continuation of AG-120 beyond disease progression will require a 2-week washout period after radiotherapy before the resumption of AG-120 treatment (see Section 9.8.1.3). Imaging should continue on schedule per protocol for these subjects and no additional CT or MRI will be required at the end of the 2-week washout period.

AG-120 should be held for the duration of palliative radiotherapy.

Hematology, serum chemistry, circulating tumor DNA, and exploratory biomarker assessments are required at both the EOT visit and at the cross over C1D1 visit. If the cross over C1D1 visit occurs within 3 days of the EOT visit, these laboratory assessments need not be repeated.

Table 3: Schedule of Assessments

Visit/Cycle:	**Pre-Screening**	**Screening**	**Cycle 1 (+/- 2 days)**		**Cycle 2 (+/- 2 days)**		**Cycle 3 (+/- 2 days)**		**Cycle 4+ (+/-2 days)**	**EOT[1]**	**Safety Followup[2]**	**PFS Follow-up[3]**	**Survival Followup**
Study Day:		**D -28**	**D1[4]**	**D15**	**D1[4]**	**D15**	**D1**	**D15**	**D1**		**D +28**		
Informed Consent		X											
Review Entry Criteria		X											
Demographics		X											
Disease History		X											
Medical and Surgical History		X											
Medication History		X											
Complete Physical Exam		X								X			
Limited Physical Exam*			X		X		X		X				
Height[5] and Weight		X								X			
ECOG PS[6]		X	X		X		X		X	X	X		
Vital Signs[7]		X	X	X	X	X	X		X	X			
12-lead ECG	Refer to Table 4 for Sampling Schedule.												
ECHO (or other methods according to institutional practice) for LVEF[8]		X											
Fresh/Banked Tumor Tissue for IDH1 Mutation Status[9]	X	X											
Laboratory Evaluations:													
Hematology[10]		X	X	X	X	X	X	X	X	X			

Serum Chemistry[11]		X	X	X	X	X	X	X	X	X			
Coagulation Studies[12]		X											

Visit/Cycle:	**Pre-Screening**	**Screening**	**Cycle 1 (+/- 2 days)**		**Cycle 2 (+/- 2 days)**		**Cycle 3 (+/- 2 days)**		**Cycle 4+ (+/-2 days)**	**EOT[1]**	**Safety Followup[2]**	**PFS Follow-up[3]**	**Survival Followup**
Study Day:		**D -28**	**D1[4]**	**D15**	**D1[4]**	**D15**	**D1**	**D15**	**D1**		**D +28**		
Urinalysis[13]		X											
Pregnancy Test[14]		X	X		X		X		X				
Registration and Treatment:													
Registration[15]		X											
Study Treatment Administration[16]			X	X	X		X		X				
Compliance Assessment[17]				X	X		X		X	X			
Tumor Assessments													
Evaluate Extent of Disease and Response to Treatment[18]		X (D -21)				X			X[19]	X[20,21]		X	
Other Clinical Assessments													
Health-Related Quality of Life Instruments[22]			X		X		X		X	X	X	X	X
Health Economic Outcomes Assessment[23]			X				X			X			
Plasma for Circulating Tumor DNA[24]		X		X	X		X		X	X			

Blood for Exploratory Biomarkers[25]		X	X		X		X		X	X			
Buccal Swab for Germ-line Mutation Analyses[26]		X											
PK/PD Assessments (Blood Sampling)	Refer to Table 4 for Sampling Schedule.												
Adverse Events[27]			X	X	X	X	X	X	X	X	X		
Visit/Cycle:	**Pre-Screening**	**Screening**	**Cycle 1 (+/- 2 days)**		**Cycle 2 (+/- 2 days)**		**Cycle 3 (+/- 2 days)**		**Cycle 4+ (+/-2 days)**	**EOT[1]**	**Safety Followup[2]**	**PFS Follow-up[3]**	**Survival Followup**
Study Day:		**D -28**	**D1[4]**	**D15**	**D1[4]**	**D15**	**D1**	**D15**	**D1**		**D +28**		
Concomitant Medications and Procedures			X	X	X	X	X	X	X	X	X		
Survival Status and New Anticancer Therapy Check													X[28]

Abbreviations: D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram, ECHO = echocardiography; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LVEF = left ventricular ejection fraction; PD = pharmacodynamic; PFS = progression-free survival; PK = pharmacokinetic; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors

Note: all cycles are 28 days (+/- 2 days) in duration, there are no planned rest periods between cycles.

* Results from the limited physical exams will be captured in source documentation, but there is no eCRF for these exams.

[1] Assessments to be conducted on the last day of study treatment (within 5 to 33 days of last dose of study treatment). For subjects who cross over from placebo arm to AG-120 after documented disease progression, their eligibility to cross over will be determined based on procedures conducted in the EOT Visit. If subjects cross over, they will follow the same assessment schedule as from C1D1.

[2] At least 28 days, and no more than 33 days after discontinuation of treatment, subjects will return to undergo review of concomitant medications, ECOG PS, and assessment for resolution of any treatment-related toxicity.

[3] Subjects who discontinue study treatment for reasons other than disease progression or withdrawal of consent will be followed every 6 weeks after the EOT Visit (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) thereafter for radiographic assessments until documented disease progression, death, start of subsequent anticancer therapy, or withdrawal of consent.

[4] Subjects are to remain at the study center for 4 hours following the C1D1 and C2D1 doses for PK/PD and ECG assessments.

[5] Height is to be obtained only at the Screening assessment.

[6] On C1D1 and cross over C1D1, assessment should be conducted pre-dose.

[7] Systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. Assessments should be conducted while the subject is seated or supine. On C1D1 and cross over C1D1, assessments should be conducted pre-dose.

[8] Procedure is to be conducted at Screening. The same procedure to evaluate LVEF should be conducted thereafter only if clinically indicated.

[9] Subjects will have most recent banked tumor (preferably within the last 3 years) or fresh biopsy samples available for IDH1m confirmation (R132C/L/G/H/S mutation variants tested) by central laboratory prior to receiving their first dose of study treatment (see Section 10.4). This sample can be collected at either Pre-screening or the Screening Visit. At least 100 microns of formalin-fixed paraffin-embedded tissue or a tumor tissue block with corresponding pathology report should be available for shipment to a laboratory designated by the Sponsor. These samples will be subjected to additional exploratory biomarker analyses. Date of tumor tissue collection for either banked or fresh tumor samples should be recorded based on the pathology report. Detailed instructions for tumor tissue collection and shipping for central testing will be provided in a separate lab manual.

[10] Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count and differential (% neutrophils, % bands), and platelet count. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date, or on cross over C1D1 if EOT assessment performed within 3 days prior to that date. On C1D1 and cross over C1D1, assessments should be conducted pre-dose.

[11] Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin. No need to repeat on C1D1 if baseline assessment performed within 3 days prior to that date, or on cross over C1D1 if EOT assessment performed within 3 days prior to that date. CA19-9 will also be collected at Screening, C1D1, Day 1 of every other cycle, and at EOT. No need to repeat CA19-9 on C1D1 or cross over C1D1 if an assessment was performed within 3 days prior to that date. On C1D1 and cross over C1D1, assessments should be conducted pre-dose.

[12] Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR).

[13] Color, appearance, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic inspection of sediment.

[14] A serum pregnancy test will be performed at Screening and a urine pregnancy test will be conducted on C1D1 and confirmed negative prior dosing, and on Day 1 of all subsequent cycles. On C1D1 and cross over C1D1, the test should be conducted pre-dose.

[15] Assign subject number and randomization allocation for eligible subjects.

[16] The morning doses on C1D1, C1D15, C2D1, C3D1, and Day 1 of all subsequent cycles are to occur in clinic to allow for pre-dose assessments (C1D1) and to accommodate PK/PD sampling (see Section 10.8 and Section 10.9).

[17] Treatment compliance is to be assessed based on return of unused drug as well as subject diaries (see Section 9.11).

[18] Tumor assessments will include all known or suspected disease sites. CT imaging of the chest, abdomen, and pelvis (Torso) with triphasic IV contrast should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT chest without IV contrast and MRI abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as Torso imaging. Bone scans will be performed at baseline if disease is suspected and on study at the same imaging time points as Torso imaging. Radiographic assessment (CT or MRI) for evaluation of disease response to be conducted at Screening (Day -21), every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) thereafter independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. For subjects randomized to placebo who receive palliative radiotherapy after unblinding and during the cross over period, a repeat CT or MRI will be performed at the end of the 2-week washout period after radiotherapy to document the area that was irradiated and to serve as the new baseline against which all subsequent RECIST v1.1 assessments will be performed, for the purpose of documenting PFS2 during the unblinded open-label cross over period (see Section 12.12.1). For subjects permitted to continue on open-label AG-120 beyond documented radiographic progression, a new baseline imaging assessment will not be required and the imaging assessments will continue on the current schedule. Any

ancillary findings on the radiographic assessments will be communicated to the appropriate physician for notification to the subject. All scans obtained will be sent to the IRC, as detailed in the site-specific Imaging Core Manual (see Section 10.7.2).

[19] Extent of disease will be assessed based on RECIST v1.1.

[20] Response to treatment is to be assessed at this visit if the subject discontinues treatment for reasons other than disease progression or start of another anticancer therapy.

[21] If a subject goes off treatment for reasons other than disease progression, response assessments will be conducted at the EOT Visit and every 6 weeks (±5 days) for the first 8 assessments (ie, through week 48), and then every 8 weeks (±5 days) thereafter until withdrawal of consent, disease progression, death, the subject is lost to follow-up, or until the end of study/study termination.

[22] EORTC-QLQ-C30, EORTC-QLQ-BIL21, and PGI-S (physical function, appetite loss, and pain) to be conducted pre-dose on C1D1 and cross over C1D1; PGI-C is not collected on C1D1 or cross over C1D1. After EOT visit, the HRQOL will be conducted every 12 weeks until the start of new anticancer therapy.

[23] EQ-5D-5L to be conducted pre-dose on C1D1 and cross over C1D1.

[24] For all subjects, plasma samples will be obtained for evaluation of IDH mutations and other genes in circulating tumor DNA at Screening, on C1D15, on Day 1 of every cycle thereafter, and at EOT. No need to repeat on cross over C1D1 if EOT assessment performed within 3 days prior to that date.

[25] For all subjects, blood samples must be obtained at Screening, on Day 1 of every cycle thereafter, and at EOT. No need to repeat on cross over C1D1 if EOT assessment performed within 3 days prior to that date.

[26] A buccal swab for germ-line mutation analysis will be obtained at Screening.

[27] Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. After informed consent has been obtained but prior to initiation of study drug, only serious adverse events (SAEs) caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs and SAEs regardless of attribution will be collected. Any SAEs that are assessed as related to study treatment that occur >28 days post-treatment also are to be reported.

[28] After a subject discontinues treatment due to progression of disease, they will be contacted every 12 weeks (±7 days) thereafter for assessment of survival status (OS), HRQOL, and anticancer therapies until death, withdrawal of consent, the subject is lost to follow-up, the occurrence of 150 OS events, or until the end of study/study termination, unless consent to participate is withdrawn.

Table 4: Pharmacokinetic/Pharmacodynamic Sampling (2-HG) and Electrocardiogram Schedule*

Visit/Cycle:	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3+**		**EOT**[1]		**Safety F/U**
Study Day:	**D -28**	**D1**		**D15**		**D1**		**D1**		**D +28**		
Assessment	**ECG**	**Blood**	**ECG**[2]	**Blood**	**ECG**[2]	**Blood**	**ECG**[2]	**Blood**	**ECG**[2]	**Blood**	**ECG**[2]	**ECG**
Pre-dose[3]	X	X	X			X	X	X[4]				
Post-dose												
Anytime									X	X	X	X
0.5 hr[5]		X				X						
2 hr[5]		X	X[6]	X	X[6]	X	X[6]					
4 hr[5]		X				X						

Abbreviations: D = day, ECG = electrocardiogram, EOT = end of treatment, F/U = follow-up.

Note: All 12-lead ECGs are to be conducted after 3 minutes of recumbency or semi-recumbency. A 12-lead single ECG should also be obtained as clinically indicated.

* The same schedule should be used for placebo subjects who cross over to AG-120 after documented disease progression.

[1] Assessments to be conducted on the last day of study treatment (within 5 days of last dose of study drug).

[2] 12-lead ECGs are to be obtained at Day 1 of Cycles 1 and 2, and on C1D15. ECGs should be done before PK sampling on these days. An ECG will be collected on C3D1 and on Day 1 of all cycles thereafter. ECGs are to be obtained within ±15 minutes of specified time.

[3] To be obtained within 30 minutes before dose; can be done any time during Screening.

[4] Blood samples to be collected at Cycle 3 and beyond, until EOT.

[5] Blood samples to be obtained within ±10 minutes of specified time. Blood samples to be collected within 10 minutes after completion of the ECG. [6] ECG to be obtained within ±15 minutes of specified time.

8.2. *Informed Consent*

A complete description of the study is to be presented to each potential subject and a signed and dated informed consent is to be obtained before any study specific procedures are performed. Subjects will sign a pre-screening and/or screening consent form depending on when their IDH1m testing is performed. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

8.3. *Demographic Data and Medical, Surgical, and Medication History*

Subject demographic data, including gender, date of birth, age, race, and ethnicity, will be obtained during Screening, according to applicable local regulations.

A complete medical and surgical history, including the site of underlying cholangiocarcinoma and the date of confirmation of the histologic diagnosis of the underlying cholangiocarcinoma, will be obtained during Screening. The medical history is to include all relevant prior medical history as well as all current medical conditions.

All medications administered and procedures conducted within 28 days prior to C1D1 should be reported in the eCRF. In addition, all prior treatment regimens for the underlying malignancy will be reported.

8.4. *Gene Mutation Analysis and Molecular Characterization*

Tissue from a pre-treatment fresh or banked tumor biopsy will be required for all screened subjects for central laboratory IDH1m confirmatory testing (R132C/L/G/H/S mutation variants tested). When subjects are enrolled for the study, these samples can be used for further molecular and/or protein analyses to gain insights into AG-120 response or resistance biomarkers. Corresponding pathology report is also required. Instructions for tumor tissue collection and shipping for central testing will be detailed in a separate study manual.

A buccal swab for germ-line mutation analysis will be obtained at Screening that can be used as a germline control for somatic mutation as well as exploring a correlation between PK variation with DME related gene polymorphisms.

For all subjects, plasma samples will be obtained for evaluation of IDH mutations and other genes in circulating tumor DNA at Screening, on C1D15, on Day 1 of every cycle thereafter, and at the EOT Visit.

8.5. *Safety Assessments*

8.5.1. *Independent Data Monitoring Committee*

Safety and other clinical data will be reviewed regularly by an IDMC to ensure the safety of therapy. The first safety review meeting will be conducted when approximately 20 subjects have completed 2 cycles of therapy or have discontinued earlier; thereafter, meetings will be conducted approximately every 3-6 months (or on an ad hoc basis) until the study is unblinded for the primary efficacy analysis. There will be no formal analysis of efficacy. Members of the IDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded to the data until the primary efficacy analysis. All summaries and analyses by treatment arm for the IDMC review will be prepared by an independent statistical group. The safety data will include demographic data, AEs, SAEs, and relevant laboratory data. Following their data review, the IDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The final decision will rest with the Sponsor.

The requirements of these reviews will be specified in the IDMC charter.

8.5.2. *Physical Examination and ECOG Performance Status*

A complete physical examination, including assessment of weight, will be obtained at Screening and at the EOT Visit. A limited physical examination should be completed on Day 1 of each treatment cycle. Height will be obtained at the Screening Visit only. Subjects should be monitored for rash at physical examinations and during assessments of adverse reactions.

Determination of ECOG PS will be performed at Screening, on Day 1 of each treatment cycle thereafter, at the EOT Visit, and at the Safety Follow-up Visit. See Appendix 15.1 for ECOG PS scoring. On C1D1 and cross over C1D1, assessment should be conducted pre-dose.

8.5.3. *Vital Signs*

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature, will be obtained at Screening, Days 1 and 15 of Cycles 1 and 2, on Day 1 of each treatment cycle thereafter, and at the EOT Visit. Assessments should be conducted while the subject is seated or supine. On C1D1 and cross over C1D1, assessments should be conducted pre-dose.

8.5.4. *Electrocardiogram and Assessment of Left Ventricular Ejection Fraction*

The 12-lead ECGs are to be obtained at Screening, pre-dose on Day 1 of Cycles 1 and 2, 2 hours post-dose on Days 1 and 15 of Cycle 1 and on Day 1 of Cycle 2, anytime on Day 1 of Cycle 3 and beyond, and at the EOT and at Safety Follow-up Visits. When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample (within 10 minutes).

All ECGs should be obtained following 3 minutes of recumbency or semi-recumbency. Subjects are to have LVEF determined by ECHO (or by other methods according to institutional practice) as clinically indicated.

8.5.5. *Safety Laboratory Assessments*

Clinical laboratory evaluations are to be performed by the site's local laboratory. Prior to starting the study, the Investigator will provide to the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory parameters to be performed by that laboratory. Clinical laboratory evaluations are to be conducted according to the Schedule of Assessments
(Table 3). Clinical laboratory evaluations may be collected up to 24 hours prior to study visit as long as the labs were collected within the visit window (+/-2 days). In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the Investigator.

The safety laboratory parameters to be evaluated by the Investigator are:

Hematology: Hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count and differential (% neutrophils, % bands), platelet count

Chemistry: Sodium, potassium, calcium, magnesium, phosphorus, albumin, glucose, blood urea nitrogen (BUN), creatinine, uric acid, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), AST, ALT, total bilirubin, direct bilirubin

Coagulation Studies: Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)

Urinalysis: Color and appearance; pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood; and microscopic inspection of sediment.

Blood for hematology and chemistries is to be obtained at Screening, on Days 1 and 15 of Cycles 1-3, on Day 1 of every treatment cycle thereafter, and at the EOT Visit. If assessments for hematology and serum chemistry were performed within 3 days prior to C1D1, these do not need to be repeated at the C1D1 Visit. If assessments for hematology and serum chemistry at EOT were performed within 3 days prior to cross over C1D1, these do not need to be repeated at the cross over C1D1 Visit. On C1D1 and cross over C1D1, assessments should be conducted predose.

CA19-9 will also be collected at Screening, C1D1, Day 1 of every other cycle starting with Cycle 3, and at EOT. If assessment of CA19-9 was performed within 3 days prior to C1D1, it does not need to be repeated at the C1D1 Visit. If assessment of CA19-9 at EOT was performed within 3 days prior to cross over C1D1, this does not need to be repeated at the cross over C1D1 Visit. On C1D1 and cross over C1D1, the test should be conducted pre-dose.

Blood samples for coagulation studies and urinalysis are to be obtained at Screening only.

Pregnancy Test: All women of child-bearing potential must have a negative pregnancy test to be eligible. A serum pregnancy test will be performed at Screening; a urine pregnancy test must be conducted and confirmed negative on the first day of study treatment administration before dosing and on Day 1 of every cycle. On C1D1 and cross over C1D1, the test should be conducted pre-dose.

8.5.6. *Adverse Events*

All AEs will be graded using the NCI CTCAE version 4.03 grading system (Appendix 15.8).

Complete details on AE monitoring are provided in Section 11.

8.6. *Exploratory Blood Samples*

Blood and/or processed blood will be requested for exploratory biomarkers and correlative studies from all subjects to assess molecular, epigenetic, and proteomic changes at Screening, on Day 1 of every cycle thereafter, and at the EOT Visit. If samples for exploratory biomarkers and correlative studies at EOT were collected within 3 days prior to cross over C1D1, these do not need to be repeated at the cross over C1D1 Visit. On C1D1 and cross over C1D1, samples should be obtained pre-dose.

Instructions for the sample collection, processing, storage, and shipment of samples for central analysis will be detailed in a separate study manual.

8.7. *Efficacy Assessments*

8.7.1. *Response to Treatment*

The efficacy of AG-120 will be evaluated by assessing response to treatment according to RECIST v1.1 (Eisenhauer, et al. 2009) (Appendix 15.9).

Radiographic assessments (CT or MRI) to obtain tumor measurements are to be conducted at Screening, every 6 weeks for the first 8 assessments (ie, through week 48), and every 8 weeks thereafter (±5 days) from C1D1, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. CT imaging of the chest, abdomen, and pelvis (Torso) with triphasic IV contrast (30 millisieverts [mSv] per scan) should be performed at baseline and on study. For subjects with allergy to IV iodine contrast, CT of the chest without IV contrast and MRI of the abdomen with IV contrast should be performed at baseline and on study. Brain scans with CT (2 mSv per scan) or MRI should be performed at baseline in subjects with known treated brain metastases and on study at the same imaging time points as Torso imaging. Bone scans (4 mSv per scan) will be performed at baseline if disease is suspected and on study as appropriate as the same imaging time points as Torso imaging. Any ancillary findings on the radiographic assessments will be communicated to the appropriate physician for notification to the subject. The same method (CT or MRI) should be used consistently for any given subject. For subjects randomized to placebo who receive palliative radiotherapy after unblinding and during the cross over period, a repeat CT or MRI will be performed at the end of the 2-week washout period after radiotherapy to document the area that was irradiated and to serve as the new baseline against which all subsequent RECIST v1.1 assessments will be performed, for the purpose of documenting PFS2 during the unblinded open-label cross over period (see Section 12.12.1). The reading radiologist(s) should be provided the dates and location of the intervening radiation when performing the new baseline assessment. For subjects permitted to continue on open-label AG-120 beyond documented radiographic progression, a new baseline imaging assessment will not be required and the imaging assessments will continue on the current schedule. For subjects who discontinue study drug for reasons other than disease progression, an assessment will be conducted at the EOT Visit and every 6 weeks through week 48, then every 8 weeks thereafter (with the exception of those subjects who initiate a new cancer therapy after discontinuing study treatment) until withdrawal of consent, disease progression, death, the subject is lost to follow-up, or until the end of study/study termination.

OS follow-up assessments will occur approximately every 12 weeks after EOT unless the subject is in PFS follow-up at that time. If a subject progresses or does not come back for scans while in PFS follow-up, then the OS follow-up assessments will begin at the next planned OS follow-up time point, following the schedule of every 12 weeks after EOT. OS follow-up will assess survival status and documentation of receipt and type of subsequent anticancer therapy unless consent to participate is withdrawn. If a subject begins a new anticancer therapy during PFS follow-up, information on the new therapy will need to be entered. OS follow-up will continue until all subjects have died, withdrawn consent, are lost to follow-up, or until the occurrence of 150 OS events, whichever occurs first. HRQOL (until the start of new anticancer therapy) assessments will be collected every 12 weeks after EOT.

All scans should be sent to the IRC, as detailed in the site-specific Imaging Core Manual (see Section 10.7.2). A central review of collected images may be conducted by an independent review committee. This independent review will not be used for treatment decisions.

8.7.2. *Independent Radiology Center*

An independent radiology review will be conducted at an independent radiology center. The IRC will be chartered to evaluate response assessment independently per RECIST v1.1.

A detailed study-specific Imaging Core Manual will be made available to sites regarding scan acquisition requirements. All radiological scans acquired at all scheduled time points and any additional (unscheduled) radiological images acquired to evaluate for potential metastatic disease also must be sent to the IRC.

8.7.3. *Health-Related Quality of Life Instruments*

Subjects will complete the EORTC-QLQ-C30, EORTC-QLQ-BIL21, and PGI-S instruments prior to dosing on C1D1; subjects will complete the EORTC-QLQ-C30, EORTC-QLQ-BIL21, PGI-C, and PGI-S prior to dosing on Day 1 of every cycle thereafter until EOT. After EOT visit, HRQOL should be assessed every 12 weeks until the start of new anticancer therapy. One additional HRQOL assessment will also be conducted at the safety follow-up visit. If subjects cross over, they will follow the same assessment schedule as from C1D1. Completion of the questionnaires takes approximately 12 to 17 minutes. During the follow-up period (PFS and/or OS), sites should follow up with subjects to encourage them to complete the HRQOL questionnaires. During this time, the HRQOL instruments will be available online as a means to minimize missing entries and lost data. If a subject does not speak one of the provided languages for the EORTC-QLQ-C30, EORTC-QLQ-BIL21, PGI-C, or PGI-S, the subject will not be required to complete the instruments. (See Section 12.8.1 for the statistical aspects for managing such missing data.)

The EORTC-QLQ-C30 is a validated general questionnaire administered to assess HRQOL in subjects with cancer. The EORTC-QLQ-BIL21 was specifically designed to measure subjectreported issues related to symptoms, disease, and treatment in subjects with cholangiocarcinoma and gallbladder cancer. The PGI-C is a self-rated evaluative instrument for assessment of change from baseline across 3 domains and the PGI-S is a self-rated evaluative instrument for current severity of symptoms across the same 3 domains. For both the PGI-C and PGI-S, subjects will be asked to respond to 3 domain functions (physical function, appetite loss, and pain) for a total of 6 questions.

8.7.4. *Health Economic Outcomes Assessment*

Subjects will complete the EQ-5D-5L prior to dosing on C1D1, C3D1, and at the EOT Visit. If subjects cross over, they will follow the same assessment schedule as from C1D1. There are index-based values ("utilities") that are a major feature of the EQ-5D-5L instrument, facilitating the calculation of quality-adjusted life years (QALYs) that are used to inform economic evaluations of healthcare interventions.

The EQ-5D-5L is a validated generic health status measure used in clinical trials in cancer that consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). The five-level version of the descriptive system will be used in this study (no problems, slight problems, moderate problems, severe problems, or extreme problems). The EQ visual analogue scale records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine."

8.8. *Pharmacokinetic Assessments*

Serial or sparse blood samples will be drawn before and after dosing of study treatment in order to determine circulating plasma concentrations of AG-120. The blood samples will also be used for the determination of 2-HG concentrations and metabolic profiling (see Section 10.9).

Blood samples will be drawn on Day 1 of Cycles 1 and 2 at the following time points: pre-dose (within 30 minutes), 30 minutes, and 2, and 4 hours (±10 minutes) post-dose. Additional blood samples for PK/PD assessments will be drawn at 2 hours (±10 minutes) post-dose on C1D15, pre-dose (within 30 minutes) on C3D1 and Day 1 of each treatment cycle thereafter, and anytime during the EOT Visit.

When the timing of a blood sample coincides with the timing of an ECG measurement, the ECG will be completed before the collection of the blood sample such that the blood sample is collected at the nominal time (±10 minutes).

8.9. *Pharmacodynamic Assessments*

Plasma samples obtained at Screening will be evaluated for 2-HG levels. Serial or sparse blood samples will be drawn at the same time as PK samples (see Section 10.8) in order to determine circulating concentrations of 2-HG.

8.10. *Sample Processing, Storage, and Shipment*

Instructions for the processing, storage, and shipment of all study samples for central analysis will be provided in a separate study manual.

ADVERSE EVENTS

Monitoring of AEs will be conducted throughout the study (once subjects have received study drug); SAEs that are assessed as related to study treatment that occur >28 days post treatment also are to be reported. All AEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). **Adverse Event Reporting Period**

Investigators will seek information on AEs at each subject contact, as outlined below. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

- After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported (eg, SAEs related to invasive study procedures such as biopsies).
- After initiation of study drug, all AEs and SAEs regardless of attribution will be collected at every visit until 28 days following the last administration of study treatment or until study discontinuation/termination or until initiation of subsequent anticancer therapy, whichever occurs first. Subjects will be assessed at the Follow-Up Visit to determine if any new AEs have occurred. After this period, Investigators should report only SAEs that are considered to be related to study treatment (AG-120/placebo).

9.1. *Definition of Adverse Events*

9.1.1. *Adverse Event*

An AE (also referred to as an adverse experience) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (eg, ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (eg, screening invasive procedures such as biopsies).

An AE can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Disease progression or death due to cholangiocarcinoma progression will not be considered an AE (or an SAE) in this study, but will be collected as an outcome or reason for discontinuation, as appropriate. Adverse events (or SAEs) considered as complications of disease progression should be reported. See Section 11.2.7 for more detailed instructions regarding the reporting of disease progression and deaths due to disease progression.

9.1.2. *Related Adverse Event*

A related AE is any AE for which there is a reasonable possibility that the drug caused the AE. **Assessment of**

Causality of Adverse Events

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study treatment, indicating "yes" or "no" accordingly (Table 5). The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of dose reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5: Causal Attribution Guidance

Is the adverse event suspected to be caused by the study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study treatment, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study treatment; and/or the AE abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon rechallenge.
NO	Adverse events will be considered related, unless they fulfill the criteria as specified below: Evidence exists that the AE has an etiology other than the study treatment (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study treatment (eg, cancer diagnosed 2 days after first dose of study treatment).

9.1.3. *Serious Adverse Event*

An AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Fatal (ie, the AE actually causes or leads to death).
- Life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect in a neonate/infant born to a mother or father exposed to study treatment.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.2. *Procedures for Reporting Adverse Events and Serious Adverse Events*

All AEs (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event (ie, a diagnosis).

For reports of SAEs, Investigators should record all case details that can be gathered promptly on the AE eCRF and submit via the Electronic Data Capture (EDC) system. All SAEs are to be reported within 24 hours from the point in time when the Investigator becomes aware of the

SAE. All SAEs must be reported whether or not they are considered causally related to AG120/placebo. Serious adverse event forms will be completed and the information collected will include subject number, a narrative description of the event, and an assessment by the
Investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or Medical Monitor.

In the event that the EDC system is unavailable, a paper SAE and fax coversheet should be completed and faxed/emailed to Agios Pharmaceuticals, Inc. (Agios) within no more than 24 hours after learning of the event using the fax numbers provided to Investigators in the Serious Adverse Event Report Form Completion Guidelines.

If there are serious, unexpected related AEs associated with the use of AG-120/placebo, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. The local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be promptly notified based on local regulations where required by the IRB/IEC of all serious, unexpected related AEs involving risk to human subjects.

All AEs, whether serious or not, will be described in the source documents and on the AE page of the eCRF. All new events, as well as those that worsen in severity or frequency relative to baseline, which occur after subjects have received at least one dose of study treatment through 28 days following the last dose of study treatment, must be recorded. Adverse events that are ongoing at the time of treatment discontinuation should be followed through the 28-day posttreatment assessment. In addition, SAEs that are assessed by the Investigator as related to study drug must be reported any time the Investigator becomes aware of such an event, even if this occurrence is more than 28 days after the last dose of study treatment.

Information to be reported in the description of each AE includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- Whether the event is serious or not
- Severity of the event (see below for definitions)
- Relationship of the event to study treatment (see below for definitions)
- Action taken: none; change in the study treatment administration (eg, temporary interruption in dosing); drug treatment required; non-drug treatment required; hospitalization or prolongation of hospitalization required (complete SAE page); diagnostic procedure performed; subject discontinued from the study (complete End of Study Visit)
- Outcome: subject recovered without sequelae; subject recovered with sequelae; event ongoing; subject died (notify the Medical Monitor within 24 hours, and complete the SAE form)

Severity of all AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to the NCI CTCAE version 4.03 (Appendix 15.8). Adverse events not listed by the NCI CTCAE will be graded as follows:

- Mild: the event is noticeable to the subject but does not interfere with routine activity.
- Moderate: the event interferes with routine activity but responds to symptomatic therapy or rest.
- Severe: the event significantly limits the subject's ability to perform routine activities despite symptomatic therapy.
- Life-threatening: an event in which the subject was at risk of death at the time of the event.
- Fatal: an event that results in the death of the subject.

9.2.1. *Diagnosis versus Signs and Symptoms*

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.2.2. *Adverse Events Occurring Secondary to Other Events*

In general, AEs occurring secondary to other events (eg, cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

a. If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
b. If vomiting results in severe dehydration and requires treatment, both events should be reported separately on the eCRF.
c. If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
d. If dizziness leads to a fall and subsequent fracture, all 3 events should be reported separately on the eCRF.
e. If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
f. If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

9.2.3. *Adverse Events of Special Interest*

An AESI can be serious or nonserious and is an event of special interest to the Sponsor. Ongoing monitoring and rapid communication (within 24 hours) by the Investigator to the Sponsor is required to allow for further characterization and reporting to regulatory authorities.

9.2.3.1. QTcF Prolongation

Any QT prolongation event assessed as Grade 2 or worse (e.g., QTcF interval longer than 480 msec or 60 msec or longer than the reading at baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), irrespective of the seriousness of the event, should be reported as an AESI to the Sponsor within 24 hours. See Section 9.9 for further details on managing subjects with QTcF Prolongation. See Appendix 15.4 for Fridericia's formula.

9.2.4. *Persistent or Recurrent Adverse Events*

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens in intensity or grade.

When an AE becomes serious (regardless of changes in grade or severity), the eCRF should be updated to reflect this. As such, a new AE (serious event with onset date for when AE became serious) should be added to the eCRF.

However the same does not hold true for AEs that change from serious to non-serious events. When an AE does not resolve but is downgraded from a serious to a non-serious event, a new AE is not required to be captured on the eCRF. A resolution date is required to be entered on the SAE form once an AE changes from a serious to non-serious event since this would result in the SAE resolving.

A recurrent AE is one that resolves between subject evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

9.2.5. *Abnormal Laboratory Values*

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

a. Accompanied by clinical symptoms
b. Results in a change in study treatment (eg, dosage modification, treatment interruption, or treatment discontinuation)
c. Results in a medical intervention (eg, potassium supplementation for hypokalemia) or a change in concomitant therapy
d. Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (ie, cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range.

9.2.6. *Deaths*

Deaths occurring during the protocol-specified AE reporting period (Section 11.2) that are attributed by the Investigator solely to progression of cholangiocarcinoma should be recorded only on the Treatment and Study Discontinuation eCRFs. All other on-treatment deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and reported to the Sponsor within 24 hours.

Death should be considered an outcome and not a distinct event. The underlying medical diagnosis or suspected diagnosis that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only 1 such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (eg, after autopsy), "unexplained death" should be replaced by the established cause of death.

All deaths will be collected. All on-treatment deaths (within the 28 days after last dose of study treatment) should have an associated SAE captured for the event that led to death, except in the event of disease progression (see Section 11.2.7).

During post-treatment survival follow-up, all deaths will continue to be collected, but only those unrelated to disease progression will be classified as SAEs.

9.2.7. *Progression of Cholangiocarcinoma*

Progression of cholangiocarcinoma should not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST v1.1 (Appendix 15.9). Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the subject's underlying cholangiocarcinoma, or does not fit the expected pattern of progression for the disease. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

9.2.8. *Pre-existing Medical Conditions*

A preexisting medical condition is one that is present at the Screening Visit for this study. Such conditions should be recorded on the Medical History eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

9.2.9. *Hospitalization or Prolonged Hospitalization*

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 11.1.3), except as outlined below.

The following hospitalization scenarios are **not considered** to be SAEs:

- Hospitalization for respite care
- Standard procedure for protocol therapy administration; however, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Administration of blood or platelet transfusion as routine treatment of studied indication; however, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling); however, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE
- A procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF; hospitalization or prolonged hospitalization for a complication remains a reportable SAE
- An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline

9.2.10. *Overdose or Incorrect Administration*

Study treatment overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects.

Any study treatment overdose or incorrect administration of study treatment should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor by the Investigator within 24 hours after learning of the event.

9.3. *Pregnancy Reporting*

Pregnancy is neither an AE nor an SAE, unless a complication relating to the pregnancy occurs (eg, spontaneous abortion, which may qualify as an SAE).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or partner of a male subject occurring while the subject is on study treatment, or within 28 days of the subject's last dose of study treatment, are considered immediately reportable events. If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the
Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. In pregnant female subjects, study treatment is to be discontinued immediately and the subject instructed to return any unused study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately using the pregnancy reporting form. The Investigator must follow-up and document the course and outcome of all pregnancies even if the subject was discontinued from the study or if the study has finished. The female subject or partner of a male subject should receive any necessary counseling regarding the risks of continuing the pregnancy and the possible effects on the fetus. Monitoring should continue until conclusion of the pregnancy.

All outcomes of pregnancy (from a female subject or the sexual partner of a male subject) must be reported by the Investigator to the Sponsor or Medical Monitor on a pregnancy reporting form within 28 days after he/she has gained knowledge of the delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (eg, maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

Females of reproductive potential must have a negative serum pregnancy test prior to the start of therapy, or a confirmation from an obstetrician in case of equivocal serum pregnancy results. Women of reproductive potential, as well as fertile men and their partners who are female with reproductive potential, must agree to use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug. Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy or bilateral oophorectomy or who have not been naturally postmenopausal (ie, who have not menstruated at all) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Males with partners who are female with reproductive potential must agree that they or their partners will use 2 effective forms of contraception (including at least 1 barrier form) when engaging in reproductive sexual activity throughout the study, and will avoid conceiving for 90 days after the last dose of study treatment.

Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization. Please refer to Section 9.13.4 for further details on potential drug-drug interactions with hormonal contraceptives.

9.4. *Follow-up of Subjects After Adverse Events*

9.4.1. *Investigator Follow-Up*

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered related to study treatment or trial-related procedures until a final outcome can be reported.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 11.3.

9.4.2. *Sponsor Follow-up*

For SAEs, AEs of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.4.3. *Post-study Adverse Events*

At the treatment discontinuation visit, the Investigator should instruct each subject to report to the Investigator any subsequent AEs that the subject's personal physician believes could be related to prior study treatment or study procedures.

The Investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a subject has discontinued study participation if the event is believed to be related to prior study treatment or study procedures. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a subject that participated in this study.

STATISTICAL METHODS

10.1. *General Methods*

Summaries will be produced for disposition, demographic and baseline disease characteristics, safety and tolerance, pharmacokinetics, PD biomarkers, and efficacy variables, as appropriate. Categorical data will be summarized by frequency distributions (number and percentages of subjects). Continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Time-to-event endpoints will be estimated using Kaplan-Meier methods. Point estimates and 95% CIs will be provided where appropriate, and estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6month, and 12-month rates) will be produced. All data will be provided in by-subject listings.

The study data will be analyzed and reported in the primary clinical study report (CSR) based on all subjects' data up to the time when 131 PFS events have been determined by Investigator assessment. Any additional data for survival follow-up and for subjects continuing to receive study treatment past the data cutoff date for the CSR until the occurrence of 150 OS events will be reported at the end of the study in the final CSR.

10.2. *Sample Size Estimation*

A total of approximately 186 subjects will be needed for the study.

The primary objective of the study is to demonstrate the improvement in PFS by IRC assessment for subjects receiving treatment with AG-120 as compared to subjects receiving placebo. Assuming a hazard ratio (HR) of 0.5 for PFS (equivalent to a median PFS of 3 months in the placebo arm versus 6 months in the AG-120 arm, assuming an exponential distribution), a total of 131 PFS events are required to provide 96% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis (Section 12.7.1) using a stratified log-rank test. Based on this, a total of approximately 186 subjects will need to be randomized in a 2:1 ratio to the AG120 and placebo arms, respectively, assuming approximately a 22% dropout rate, an approximate 26-month randomization period, and an additional 6-month follow-up for PFS after the last subject is randomized. Therefore, the primary analysis of PFS will occur at approximately 6 months after the last subject is randomized.

Overall survival will be analyzed twice, once at the time of the final analysis for PFS and once at the occurrence of 150 OS events (final analysis for OS, which will occur at approximately 24 months after the last subject is randomized). Assuming an HR of 0.67 for OS (median OS of 8 months in the placebo arm vs. 12 months in the AG-120 arm, assuming an exponential distribution), a total of 150 OS events will provide 64% power at a 1-sided alpha of 0.025.

10.3. *Analysis Sets*

The following analysis sets will be evaluated and used for presentation of the data:

- Intend-to-Treat Analysis Set (ITT): All subjects who were randomized. Subjects will be classified according to the assigned treatment arm. The ITT will be used for the primary efficacy analyses, and is the default analysis set unless otherwise specified.
- Safety Analysis Set (SAS): All subjects who received at least one dose of study treatment. Subjects will be classified according to the treatment received. The SAS will be the primary set for the analysis of safety data, unless otherwise specified.

- Per-Protocol Set (PPS): All subjects in the ITT who had no major protocol violations. Additional efficacy analyses may be produced using the PPS. Rules for major protocol violations will be specified in the statistical analysis plan (SAP).
- Pharmacokinetic Analysis Set (PAS): All subjects who have at least 1 blood sample post-dose providing evaluable PK data for AG-120.

10.4. *Randomization and Stratification*

Eligible subjects will be randomized in a 2:1 ratio to receive AG-120 or placebo, stratified by number of prior therapies (1 vs 2). The randomization scheme will be generated by an independent statistical group. The randomization assignment will be implemented by an interactive web response system (IWRS).

10.5. *Disposition*

A tabulation of the disposition of subjects will be presented by treatment arm, including the number randomized, the number treated, the reasons for treatment discontinuation, and the reasons for study discontinuation. Entry criteria and protocol deviations will be listed.

10.6. *Baseline Evaluations*

Demographic and baseline disease characteristic data will be summarized by treatment arm. Data to be tabulated will include sex, age, and race and ethnicity, as well as disease-specific information.

10.7. *Efficacy Analyses*

Response to treatment will be assessed by the site Investigators and by the IRC using RECIST v1.1 (see Section 10.7).

To control the overall Type I error rate at the 5% level, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple statistical testing of the primary and selected secondary efficacy endpoints. These endpoints will be tested in the following order:

- PFS based on IRC
- OS
- ORR based on IRC

No adjustment to the α level will be made for the other analyses.

10.7.1. *Analysis for the Primary Endpoint*

The primary endpoint of PFS is defined as the time from the date of randomization to the date of first documentation of disease progression as determined by the IRC per RECIST v1.1 or death due to any cause, whichever occurs first.

Subjects without documentation of disease progression or death at the time of the primary analysis of PFS will be censored at the date of the last response assessment prior to the start of alternate therapy. If disease progression or death is documented after 1 single missing response assessment, the actual event date of disease progression/death will be used for the PFS event date. If disease progression is documented after 2 or more missing response assessments, the PFS time of these subjects will be censored at the date of the last response assessment (CR or PR or SD) prior to 2 or more missing response assessments. Detailed censoring rules will be specified in the SAP.

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment arms using a log-rank test stratified by the randomization stratification factor at onesided 2.5% level of significance. Assuming a proportional hazard model for PFS, the null hypothesis will be tested:

$$H_{01} \text{ (null hypotheses): } \Theta_1 \geq 0 \text{ vs. } H_{a1} \text{ (alternative hypotheses): } \Theta_1 < 0$$

where $\Theta_1$is the log hazard ratio of PFS in the AG-120 (investigational treatment) arm vs. placebo (control) arm.

A Cox regression model stratified by the randomization stratification factor will be used to estimate the HR of PFS comparing the AG-120 arm with the placebo arm, along with the 95% CI.

Kaplan-Meier estimates of PFS, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be presented for each treatment arm. Patterns of censored data will be examined between the treatment arm and placebo arm by summarizing the number of PFS events that are censored and by tabulating the reasons for censored observations.

There will be no interim analysis for PFS. The analysis of PFS will be performed when 131 Investigator-assessed PFS events have occurred, expected at approximately 32 months after the first subject is randomized in the study. The primary analysis of PFS will be based on IRC response assessments.

Sensitivity analyses for PFS may include but are not limited to the tests listed below. PFS may be analyzed using:

1. Stratified log-rank test using the PPS based on Investigator assessments;
2. Stratified log-rank test using the PPS based on IRC assessments;
3. Unstratified log-rank test using the ITT based on Investigator assessments;
4. Unstratified log-rank test using the ITT based on IRC assessments.

Other sensitivity analyses for PFS may be conducted and will be specified in the SAP.

Subgroup analyses will be performed on each level of the stratification factor. The analyses will include Kaplan-Meier summaries, unstratified log-rank tests and HRs (together with associated 95% CIs) from Cox regression models. Other subgroup analyses for PFS, including but not limited to locally advanced vs. metastatic cancer, may be conducted and will be specified in the SAP.

10.7.2. *Analyses for the Secondary Efficacy Endpoints*

10.7.2.1. Overall Survival

Overall survival is defined as the time from date of randomization to the date of death due to any cause. Subjects who are alive at the analysis cutoff date will be censored at the date of last contact.

Assuming an HR of 0.67 for OS (median OS of 8 months in the placebo arm vs. 12 months in the AG-120 arm, assuming an exponential distribution), a total of 150 OS events will provide 64% power at a 1-sided alpha of 0.025. With a sample size of 186, additional OS follow-up of approximately 24 months after last subject is randomized will be needed to obtain 150 OS events. Assuming an HR of 0.615 (median OS of 8 months in the placebo arm vs. 13 months in the AG-120 arm, assuming an exponential distribution), a total of 150 OS events will provide 80% power at a 1-sided alpha of 0.025.

Due to the allowance of cross over of subjects who progress on the placebo arm to the AG120 arm, it is anticipated that the true effect of AG-120 on survival as compared to placebo will not be able to be measured, and that the trial will not be powered to detect a meaningful survival effect.

OS will be compared between the two treatment arms, provided the primary endpoint PFS is statistically significant favoring the AG-120 arm. A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. OS will be analyzed based on the data from the ITT, according to the treatment arm to which subjects were randomized and the strata they were assigned at randomization. The distribution function of OS will be estimated using the KaplanMeier method. The median OS along with 95% CIs will be presented by treatment arm. Assuming a proportional hazards model for OS, the null hypothesis will be tested:

$$H_{02} \text{ (null hypotheses): } \Theta_2 \geq 0 \text{ vs. } H_{a2} \text{ (alternative hypotheses): } \Theta_2 < 0$$

where Θ_2 is the log hazard ratio of OS in the AG-120 (investigational treatment) arm vs. placebo (control) arm.

Two analyses are planned for OS: 1) an interim analysis at the projected time of the final analysis for PFS (provided PFS is significant); 2) a final analysis for OS when 150 deaths are observed. Overall survival at the interim will be tested with the alpha being determined using the gamma spending function (gamma=-8), and the overall type I error rate will be controlled at the 1-sided 0.025 level. The log-rank test stratified by randomization stratification factor will be used to compare OS between the two treatment arms. The unstratified log-rank test will also be conducted.

Kaplan-Meier estimates of OS will be presented for each treatment arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12month rates). The HR of OS with 95% CI comparing AG-120 with placebo will be estimated from a Cox proportional hazards model stratified by randomization stratification factor.

Duration of follow-up will also be presented.

Sensitivity analyses for OS, such as taking into account the factor of cross over, will be specified in the SAP.

10.7.2.2. Progression Free Survival per Investigator

The secondary endpoint of PFS is defined as the time from randomization to the first occurrence of documented disease progression as determined by the Investigator and the institutional radiologist(s) per RECIST v1.1 or death from any cause, whichever occurs first.

The same censoring rules as the primary endpoint of PFS will be applied to PFS per Investigator.

A log-rank test stratified by the randomization stratification factor will be used to compare the PFS between the AG-120 vs. placebo arm. A Cox regression model stratified by the randomization stratification factor will be used to estimate the HR of PFS comparing the AG-120 arm with the placebo arm, along with the 95% CI.

Kaplan-Meier estimates of PFS, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates), will be presented for each treatment arm.

10.7.2.3. Objective Response Rate

For the secondary efficacy endpoints of ORR, DOR, and TTR, analyses will be performed using Investigator- and IRC-assessed response.

Objective response rate is defined as the rate of confirmed CR and PR per RECIST v1.1.

A summary of best objective response by arm will be produced. A Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between the 2 treatment arms. A logistic regression model may be used to estimate the treatment effect in terms of an odds ratio. The odds ratio and its associated 95% CIs will be presented.

10.7.2.4. Duration of Response

Among responders who achieve confirmed CR or PR, DOR will be calculated from the date of the first occurrence of response to the date of first documented disease progression or death. Kaplan-Meier methods will be used to estimate DOR; subjects without progression or death will be censored at the last response assessment date. Detailed censoring rules will be included in the SAP.

Kaplan-Meier estimates of DOR will be presented by arm, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6-month, and 12-month rates).

10.7.2.5. Time to Response

Among responders, time to response will be assessed from the date of randomization to the date of first occurrence of confirmed response per RECIST v1.1. TTR will be tabulated by arm.

10.8. *Analyses of Health-Related Quality of Life and Health Economic Outcomes*

10.8.1. *Health-Related Quality of Life Analyses*

The EORTC-QLQ-C30, EORTC-BIL21, PGI-C, and PGI-S questionnaires will be used to collect data on the subject's functioning, disease-related symptoms, HRQOL, and health status. If a subject is not able to speak any language that is covered by the EORTC-QLQ-C30, EORTCQLQ-BIL21, PGI-C, or PGI-S, the data from those instruments will be missing throughout the duration of that subject's involvement in the study. The number and percentage of subjects with the entire questionnaire missing will be summarized by treatment. Details including the missing data handling will be specified in the SAP.

Descriptive statistics (eg, means and medians) will be used to summarize the individual items and sub-scale scores of HRQOL data as well as PGI-C and PGI-S scores at each scheduled assessment time point by treatment. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized by treatment. A repeated measurements analysis model may be used to compare the two treatment groups with respect to changes in the HRQOL domain scores as well as the PGI-C and PGI-S scores longitudinally over time. In addition, anchor-based method will be used to analyze the key domains with the specific anchor questions (PGI-C and PGI-S).

Detailed analysis plan will be specified in the SAP.

10.8.2. *Health Economic Outcomes Analyses*

EQ-5D-5L scores will be summarized by descriptive statistics for treatment arms.

10.9. *Exposure and Safety Analyses*

Safety will be evaluated by the incidence of AEs, causality, severity, seriousness, and type of AEs, and by the subject's vital signs, ECOG performance scores, clinical laboratory test results, ECG, and LVEF data (as clinically indicated).

A summary of study drug exposure, including total dose, duration of treatment, dose intensity, and the proportion of subjects with dose modifications will be summarized by treatment arm. Reasons for dose modifications will be listed by subject and summarized.

Concomitant medications will be listed by subject and will be summarized by treatment arm.

All safety data will be listed by subject and summarized by treatment arm.

10.9.1. *Adverse Events*

Summary tables and listings for adverse events will include treatment-emergent adverse events (AEs), where AE is defined as any AE that occurred between the first dose of any study drug and 28 days following the last dose of any study drug. The incidence of AEs (new or worsening from baseline) will be summarized according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class and/or preferred term, severity (based on NCI CTCAE v4.03 grading as assessed by the Investigator), seriousness, and relation to study treatment. The following summaries will be produced:

- All AEs
- AEs leading to dose modifications
- Treatment-related AEs
- Grade 3 or higher AEs
- Grade 3 or higher treatment-related AEs
- The most commonly reported AEs (ie, those events reported by ≥10% of all subjects)
- SAEs
- Discontinuations due to AEs

By-subject listings will be provided for on-treatment deaths (on-treatment is defined as the period starting from the first dose to 28 days after the last dose), AEs, SAEs, and AEs leading to discontinuation of treatment.

10.9.2. *Laboratory Abnormalities*

For laboratory tests included in the NCI CTCAE version 4.03, laboratory data will be graded accordingly; a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following summaries will be generated separately for hematology, serum chemistry and coagulation studies, and urinalysis laboratory tests:

- Descriptive statistics for the actual values and/or change from baseline of clinical laboratory parameters over time.
- Shift tables using NCI CTCAE grades to compare baseline to the worst on-treatment value (for laboratory tests where NCI CTCAE grades are not defined, shift tables using the low/normal/high/[low and high] classification to compare baseline to the worst on-treatment may be generated).
- Listing of all laboratory data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, graphical displays of key safety parameters, such as scatter plots of actual or change in laboratory tests over time or box plots may be specified in the SAP.

10.9.3. *Other Safety Data*

Descriptive statistics for the actual values and/or the changes from baseline of vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) over time will be summarized.

Descriptive statistics of ECOG PS over time will be summarized by frequency. Shift tables may be provided for ECOG PS from baseline to worst value of post-baseline assessments.

Categorical analysis of QTcF intervals may be performed. Maximum QTcF intervals and maximum changes from baseline may also be summarized similarly in a separate display. ECG abnormalities if collected will be presented in a data listing.

Additional safety analyses may be performed if deemed necessary.

10.10. *Pharmacokinetic Analyses*

A population pharmacokinetics approach will be performed to assess typical and individual subject PK parameters. Descriptive statistics will be used to summarize PK concentrations at different nominal time points across subjects.

10.11. *Pharmacodynamic Analyses*

Descriptive statistics will be used to summarize 2-HG concentrations at different nominal time points across subjects. The potential relationship between plasma exposure of AG-120 and plasma 2-HG levels will be explored with descriptive and graphical methods as appropriate.

10.12. *Exploratory Analyses*

10.12.1. *Analysis of PFS2*

For subjects who cross over from the placebo arm to the AG-120 arm, PFS2 will be calculated from first dose of AG-120 to second documented disease progression per Investigator (or death). The new baseline for response assessment for subjects who crossed over will be the progressive disease scan prior to cross over. For subjects who cross over who receive palliative radiotherapy after unblinding and during the cross over period, the new baseline for response assessment will be the MRI or CT scan obtained at the end of the 2-week washout period after radiotherapy. In the event that more than 1 scan is obtained, the latest scan prior to the first dose of AG-120 will be used as the new baseline. Kaplan-Meier estimates of PFS2 will be presented, including estimates of the median and other quantiles, as well as individual time points (eg, 3-month, 6 month, and 12-month rates).

10.12.2. *Other Exploratory Analyses*

All subjects with evaluable sample measurements will be included in the data analysis. Actual values or changes/shifts from baseline of exploratory PK or PD biomarker data will be summarized over time and may be displayed graphically.

All exploratory PK or PD biomarker data collected will be listed in full, and other exploratory analyses may be conducted depending on the data. If feasible, these may include exploratory PK/PD analyses and exploratory correlation analyses with clinical response or outcomes.

There may be circumstances when a decision is made to stop collection, not perform, or discontinue the analysis of PD biomarker samples due to either practical or strategic reasons (eg, inadequate sample numbers, issues related to the quality of samples, or issues related to the assay that precludes the analysis of samples). Under such circumstances, the sample size may be too small to perform any data analysis and the available data will only be listed.

All exploratory analyses intended to be discussed in the CSR will be defined in the SAP. Additional analyses may be planned and reported separately from this study.

10.13. *Procedures for Handling Missing, Unused, and Spurious Data*

No imputation will be performed for missing data elements unless specified otherwise.

When tabulating AE data, partial dates will be imputed. Rules of imputation will be specified in the SAP.

For the purposes of reporting, subjects who have no disease progression (or death) by data cutoff date will have time-to-event data (eg, DOR and PFS) censored at the date of last documented disease assessment prior to the data cutoff date. Further details of censoring rules for analyses of efficacy will be documented in the SAP.

Subjects who have disease progression and continue to receive treatment after progression will be considered as having documented progressive disease at the time of first progression and will be counted as progressive disease at that time in primary clinical activity analyses. All response assessments occurring after documented

progression may be listed and analyzed separately, except for subjects who were on the placebo arm and crossed over to the AG-120 arm after documented disease progression, whose response assessment after cross over will be used to calculate PFS2.

10.14. *Interim Analyses*

Interim safety reviews of unblinded data will be conducted by the IDMC as outlined in the IDMC charter. No formal interim efficacy analysis will be conducted prior to the primary analysis for this study.

ADMINISTRATIVE REQUIREMENTS

11.1. *Good Clinical Practice*

The study will be conducted in accordance with the International Council for Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and Investigators' Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

11.2. *Ethical Considerations*

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (WMA 1996).

The Investigator must obtain IRB/IEC approval for the investigation and must submit written documentation of the approval to the Sponsor before he or she can enroll any subject into the study. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC. The IRB/IEC is to be notified of any amendment to the protocol in accordance with local requirements. Progress reports and notifications of serious unexpected adverse drug reactions are to be provided to the IRB/IEC according to local regulations and guidelines.

11.3. *Subject Information and Informed Consent*

The Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her legal representative prior to study participation.

The subject's signed and dated informed consent must be obtained before conducting any studyrelated procedures. The Investigator must maintain the original, signed consent form. A copy of the signed form must be given to the subject.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

11.4. *Subject Confidentiality*

In order to maintain subject privacy, all source documents/eCRFs, study treatment accountability records, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.5. *Protocol Compliance*

The Investigator will conduct the study in compliance with the protocol. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable, where regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The Sponsor or designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or Medical Monitor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

11.6. *Data Management*

All data for the subjects recruited for the trial will be entered onto the eCRFs via an EDC system provided by the Sponsor or designee. Only authorized staff may enter data onto the eCRFs. If an entry error is made, the corrections to the eCRFs will be made according to eCRF guidelines by an authorized member of the site staff.

Electronic case report forms will be checked for correctness against source document data by the Sponsor's monitor. If any entries into the eCRF are incorrect or incomplete, the monitor will ask the Investigator or the study site staff to make appropriate corrections, and the corrected eCRF will again be reviewed for completeness and consistency. Any discrepancies will be noted in the eCRF system by means of electronic data queries. Authorized site staff will be asked to respond to all electronic queries according to the eCRF guidelines.

11.7. *Source Document/Case Report Form Completion*

Source documents/eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/eCRF. The source document/eCRF should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents.

11.8. *Direct Access to Source Data*

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the source documents/eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, e-mail, and fax).

All unused study treatment and other study materials should be destroyed or returned to the Sponsor or designee after the study has been completed.

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, eCRFs, and other study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

11.9. *Record Retention*

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to

applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

11.10. *Liability and Insurance*

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

11.11. *Publication of Study Findings and Use of Information*

All information regarding AG-120 supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of AG-120 and a companion diagnostic device and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

LIST OF REFERENCES

ACS. Bile Duct Cancer (Cholangiocarcinoma). 2014: American Cancer Society.

AJCC, ed. 2010 AJCC Cancer Staging Manual: 7th edition: American Joint Committee on Cancer.

Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH1 and IDH2 mutations are frequent events in central chondrosarcoma and central and periosteal chondromas but not in other mesenchymal tumours. *J Pathol.* 2011;224(3):334-43.

Borger DR, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Straley KS, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broadbased tumor genotyping. *Oncologist.* 2012;17(1):72-9.

Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-Enterologues Oncologues. *Cancer.* 2015;121(18):3290-7.

Chowdhury R, Yeoh KK, Tian YM, Hillringhaus L, Bagg EA, Rose NR, et al. The oncometabolite 2-hydroxyglutarate inhibits histone lysine demethylases. *EMBO Rep.* 2011;12(5):463-9.

Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature.* 2009;462(7274):739-44.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-47.

EORTC. EORTC QLQ-C-30 Scoring Manual, Version 3.0. *EORTC QOL Group.* 1995.

Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell.* 2010;18(6):553-67.

Friend E, Yadegarfar G, Byrne C, Johnson CD, Sezer O, Pucciarelli S, et al. Development of a questionnaire (EORTC module) to measure quality of life in patients with cholangiocarcinoma and gallbladder cancer, the EORTC QLQ-BIL21. *Br J Cancer.* 2011;104(4):587-92.

Geisbrecht BV, and Gould SJ. The human PICD gene encodes a cytoplasmic and peroxisomal NADP(+)-dependent isocitrate dehydrogenase. *J Biol Chem.* 1999;274(43):30527-33.

Goyal L, Govindan A, Sheth RA, Nardi V, Blaszkowsky LS, Faris JE, et al. Prognosis and Clinicopathologic Features of Patients With Advanced Stage Isocitrate Dehydrogenase (IDH) Mutant and IDH Wild-Type Intrahepatic Cholangiocarcinoma. *Oncologist.* 2015;20(9):1019-27.

Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, et al. Cancerassociated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med.* 2010;207(2):339-44.

Kipp BR, Voss JS, Kerr SE, Barr Fritcher EG, Graham RP, Zhang L, et al. Isocitrate dehydrogenase 1 and 2 mutations in cholangiocarcinoma. *Hum Pathol.* 2012;43(10):1552-8.

Koivunen P, Lee S, Duncan CG, Lopez G, Lu G, Ramkissoon S, et al. Transformation by the (R)-enantiomer of 2-hydroxyglutarate linked to EGLN activation. *Nature.* 2012;483(7390):484-8.

Lamarca A, Hubner RA, David Ryder W, and Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann Oncol.* 2014;25(12):2328-38.

Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. *Nature.* 2012;483(7390):4748.

Morganroth J. Focus on issues in measuring and interpreting changes in the QTc interval duration. *Eur J Heart Suppl.* 2001;3(Suppl K):K105-K111.

RARECARE. Surveillance of rare cancers in Europe: Cholangiocarcinoma. 2016.

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood.* 2010;116(20):4045-59.

Saha SK, Parachoniak CA, Ghanta KS, Fitamant J, Ross KN, Najem MS, et al. Mutant IDH inhibits HNF-4alpha to block hepatocyte differentiation and promote biliary cancer. *Nature.* 2014;513(7516):110-4.

Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.

Szende A, Janssen, B., Cabases, J., ed. 2014 Self-Reported Population Health: An International Perspective based on EQ-5D: Springer Netherlands.

Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. *Nature.* 2012;483(7390):479-83.

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273-81.

Wang F, Travins J, DeLaBarre B, Penard-Lacronique V, Schalm S, Hansen E, et al. Targeted Inhibition of Mutant IDH2 in Leukemia Cells Induces Cellular Differentiation. *Science.* 2013;In press.

Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Coller HA, et al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. *Cancer Cell.* 2010;17(3):225-34.

Welch JS, Ley TJ, Link DC, Miller CA, Larson DE, Koboldt DC, et al. The origin and evolution of mutations in acute myeloid leukemia. *Cell.* 2012;150(2):264-78.

Westfall PH, and Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *Journal of Statistical Planning and Inference.* 2001;99(1):25-40.

WMA. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. 1996.
https://www.medunigraz.at/ethikkommission/Forum/Download/Files/DoH_1996_EN.pdf.

Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. *Cancer Cell.* 2011;19(1):17-30.

Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360(8):765-73.

Yen KE, Bittinger MA, Su SM, and Fantin VR. Cancer-associated IDH mutations: biomarker and therapeutic opportunities. *Oncogene.* 2010;29(49):6409-17.

Yoshihara T, Hamamoto T, Munakata R, Tajiri R, Ohsumi M, and Yokota S. Localization of cytosolic NADP-dependent isocitrate dehydrogenase in the peroxisomes of rat liver cells: biochemical and immunocytochemical studies. *J Histochem Cytochem.* 2001;49(9):1123-31.

APPENDICES

13.1. *Eastern Cooperative Oncology Group Performance Status Scoring*

Grade	Symptomatology
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.

13.2. *Prohibited Concomitant Medications*

Prohibited medications and certain foods are not allowed in this study while subjects are receiving study drug.	
Strong CYP3A Inducers	**CYP3A Substrates with a Narrow Therapeutic Window**
Avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole[6], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine[1]

Note that this is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm08
0499.htm
"CYP substrates with a narrow therapeutic window" refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

13.3. *New York Heart Association Classification*

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.

[6] Withdrawn from the United States market because of safety reasons.

IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

13.4. *Fridericia's Formula*

$QTcF=QT/RR^{1/3}$

13.5. *Medications Known to Prolong the QT Interval*

amiodarone	dofetilide	grepafloxacin	moxifloxacin	quinidine
astemizole	dolasetron	halofantrine	norfloxacin	sevoflurane
azithromycin	domperidone	haloperidol	ofloxacin	sotalol
bepridil	droperidol	ibutilide	ondansetron	sparfloxacin
chloroquine	erythromycin	itraconazole	palonosetron	terfenadine
chlorpromazine	escitalopram	ketoconazole	pentamidine	thioridazine
ciprofloxacin	flecainide	levofloxacin	pimozide	voriconazole
citalopram	gatifloxacin	levomethadyl	posaconazole	
clarithromycin	gemifloxacin	mesoridazine	probucol	
disopyramide	granisetron	methadone	procainamide	

For a complete and updated (ongoing) list of medications, please use the following link: https://crediblemeds.org/healthcare-providers/

13.6. *Examples of Strong and Moderate CYP3A4 Inhibitors*

Moderate CYP3A4 Inhibitors
Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong CYP3A4 Inhibitors
Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole
Ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole
Ritonavir, saquinavir, telaprevir, telithromycin, voriconazole

Note: Based on FDA guidelines; Investigators should follow local institutional guidelines, where appropriate.

13.7. *Representative Examples of Low-Fat and High-Fat, High-Calorie Meals*

Low-fat breakfast:

A) 2 slices of white bread toast, 1 tablespoon light fat margarine, 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams of fat).

B) 1 cup of cereal, 1 slice of toast with jam, 8 ounces of skim milk, and 1 cup of decaffeinated coffee or tea (520 calories and 2 grams of fat).

A high-fat breakfast consists of the following and may be adapted to the local regional preference: 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk. This representative high-fat breakfast contains approximately 1000 calories and 58 grams of fat.

13.8. *National Cancer Institute Common Terminology Criteria for Adverse Events*

The NCI CTCAE, version 4.03, can be accessed using the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

13.9. *RECIST v1.1*

Tumor lesions are to be categorized as measurable versus non-measurable and target versus nontarget based on RECIST v1.1 (Eisenhauer, et al. 2009).

Measurable Lesions:

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm on the short axis when assessed by CT scan.

Non-measurable Lesions:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, including leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. **Target Lesions:**

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Pathological lymph nodes that are defined as measurable and identified as target lesions must have a short axis of ≥15 mm by CT scan. Only the short axis of these nodes contributes to the baseline sum.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions:

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’ or ‘unequivocal progression.’ The following criteria outlined in Table 6 and Table 7 will be used to assess response to treatment.

Table 6: Disease Response Criteria for Target and Non-target Lesions

Category	Response Criteria	
	Target Lesions	**Non-Target Lesions/Tumor Markers**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm	Disappearance of all non-target lesions, and normalization of tumor marker level All lymph nodes must be nonpathological in size (<10 mm short axis).
Partial Response (PR)	A ≥30% decrease in the sum of the diameter of target lesions, taking as reference the baseline sum diameter	N/A
Stable Disease (SD) / Incomplete Response	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since the treatment started	Persistence of 1 or more non-target lesion(s) and/or Maintenance of tumor marker levels above the normal limits
Progressive Disease	A ≥20% increase in the sum of the diameter of target lesions, taking as reference the smallest sum diameter recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm, or The appearance of 1 or more new lesions	Appearance of 1 or more new lesions, and/or Unequivocal progression of existing non-target lesions

Table 7: Overall Disease Response Criteria

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Incomplete response/Non-Progressive disease	No	PR
SD	Incomplete response/NonProgressive disease	No	SD
Progressive disease	Any	Yes or no	Progressive disease
Any	Progressive disease	Yes or no	Progressive disease
Any	Any	Yes	Progressive disease

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.