

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213736Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Memorandum**

**FROM:** Lola Fashoyin-Aje, M.D., M.P.H.  
Deputy Director (acting)  
Division of Oncology 3  
Office of Oncologic Diseases  
Office of New Drugs  
Center for Drug Evaluation and Research

**SUBJECT:** Review Designation Memo for pemigatinib

**TO:** NDA 213736

The review status of this file submitted as an original NDA is designated to be:

***Priority***

On September 30, 2019, Incyte Corporation (Incyte) submitted the above referenced New Drug Application (NDA) for pemigatinib, for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement.

Qualifying Criteria for Priority Review Designation

1. Serious Condition:

A serious condition is defined in the expanded access regulations in 21 CFR 312.300(b)(1) as follows: a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Cholangiocarcinoma (CCA) that is locally advanced or metastatic is a serious/life threatening condition. Resection is the only potentially curative option for patients with CCA. Unfortunately, only a small minority of patients have resectable tumors at the time

of diagnosis. For most patients, diagnosis is made when symptoms develop which typically occurs once the disease has progressed to a late stage (Ghouri et al., 2015). Most patients with unresectable or metastatic tumors, die within a year of diagnosis.

FGFR2 gene fusions have been observed in approximately 13-14% of intrahepatic cholangiocarcinomas (iCCA) and are more common in younger patients and in females (Churi et al., 2014; Arai et al., 2014; Graham et al., 2014). Patients with tumors harboring FGFR genetic alterations also tend to present at an earlier stage (TNM stage I/II vs. III/IV: 35.8% vs. 22%, respectively), and may experience longer survival compared with patients without FGFR genetic alterations.

## 2. Demonstrating the Potential to Be a Significant Improvement in Safety or Effectiveness:

Based on the results of the ABC-02 trial, the standard of care for patients with advanced or metastatic cholangiocarcinoma is combination chemotherapy with gemcitabine and cisplatin. In this study, 410 patients with locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer were randomized to receive either cisplatin (25 mg/m<sup>2</sup>) in combination with gemcitabine (1000/m<sup>2</sup>) administered on Days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000/m<sup>2</sup> on Days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary endpoint was overall survival (OS). After a median follow-up of 8.2 months and 327 deaths, the median OS was 11.7 months among the 204 patients in the cisplatin–gemcitabine group, and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; p=0.049) (Valle et al., 2011). Other systemic treatment options include fluoropyrimidine- or other gemcitabine-based regimens (based upon the results of phase II trials), participation in clinical trials, best supportive care, and pembrolizumab (for the treatment of patients with microsatellite instability high or mismatch repair deficient metastatic tumors).

There are currently no therapies approved for the treatment of previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement.

Incyte provided the results of Study INCB 54828-202, an open-label, single-arm, multicenter, study to demonstrate the efficacy of pemigatinib in patients with advanced/metastatic or surgically unresectable FGFR2-rearranged CCA who have disease progression after at least 1 line of prior systemic therapy. Patients received pemigatinib 13.5 mg once daily on an intermittent schedule (2 weeks on, 1 week off). Patients had previously treated, FGFR2-rearranged cholangiocarcinoma. The efficacy evaluable population included 145 of 146 enrolled participants who were assigned to cohorts based on tumor FGF/FGFR status. Enrollment and initial cohort assignment were permitted based on genomic testing results from a certified local laboratory. Final cohort assignment for statistical analysis was based on genomic testing results from the central genomics laboratory using the analytically validated Foundation Medicine CTA. Cohorts were as follows:

- Cohort A included 107 patients with FGFR2-rearranged CCA
- Cohort B included 20 patients with CCA with other FGF/FGFR alterations
- Cohort C included 18 patients with tumors that were negative for FGF/FGFR alterations.

One enrolled participant was excluded from the efficacy evaluable population because the Foundation Medicine CTA did not confirm the FGF/FGFR local laboratory result due to tissue sample failure.

The primary efficacy endpoint of Study INCB 54828-202 is ORR, defined as the proportion of participants who achieved a complete response or a partial response based on RECIST v1.1, in patients with FGFR2-rearranged CCA. The key secondary endpoint is duration of response (DOR), defined as the time from the first overall response contributing to an objective tumor response to the earlier of progressive disease based on RECIST v1.1 (Eisenhauer et al 2009) or death.

The study achieved the pre-specified threshold for a positive study outcome (lower limit of the 95% CI for ORR exceeded 15%). In the 107 participants with FGFR2-rearranged CCA (Cohort A), the IRC-assessed ORR is 35.5% (95% CI: 26.50, 45.35). Three patients (2.8%) had complete responses and 35 patients (32.7%) had partial responses. The Kaplan-Meier estimated median duration of response based on IRC assessment is 7.49 months (95% CI: 5.65, 14.49), with a minimum of 6 months of follow-up from initial response in 92% of participants who had a confirmed tumor response.

To support the safety evaluation, data from 8 clinical studies of pemigatinib administered as a single agent, including pool of 484 patients with advanced malignancies (cholangiocarcinoma population (n = 161), 466 of whom completed at least one 21-day treatment cycle, unless the participant experienced a toxicity considered at least possibly related to pemigatinib prior to completion of the first cycle (i.e., modified safety population), was submitted. However, the primary analysis of the safety of the proposed dosage regimen, is based on results from Study INCB 54828-202 (n=147). The most common treatment emergent adverse events (TEAEs), were hyperphosphatemia, alopecia, diarrhea, fatigue, nail toxicity, dysgeusia, nausea, constipation, stomatitis, dry mouth, decreased appetite, vomiting, dry eye, arthralgia, abdominal pain, hypophosphatemia, back pain, and dry skin. The majority of these events were Grade 1 or 2 in severity and considered related to pemigatinib by the investigator. Treatment-emergent events of Grade  $\geq 3$  severity occurred in 63.7% of patients in Study INCB 54828-202 and were most commonly ( $\geq 5\%$ ) events of hypophosphatemia, arthralgia, hyponatremia, and stomatitis.

In summary, the results from Study INCB 54828-202 Cohort A appear to demonstrate that treatment with pemigatinib in patients with advanced CCA yields durable responses, with ORR results and a safety profile that compare favorably to those observed with commonly used cytotoxic agents.

As stated in FDA Guidance [Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014)] and CDER MAPP 6020.3 (priority review policy), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. For the reasons stated above, I believe that this application meets the criteria for priority review.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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IBILOLA A FASHOYIN-AJE  
11/26/2019 05:24:19 AM

IND 138179

## MEETING MINUTES

Incyte Corporation  
Attention: Aaron Packman, MBA  
Senior Director, Regulatory Affairs  
1801 Augustine Cut-Off  
Wilmington, DE 19803

Dear Mr. Packman:<sup>1</sup>

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pemigatinib (INCB054828).

We also refer to the teleconference between representatives of your firm and the FDA on August 8, 2019. The purpose of the meeting was to discuss your plans to submit a proposed New Drug Application (NDA) for pemigatinib based on the top-line results of Study INCB 54828-202, entitled “A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy.” The proposed indication to be supported by these data is for the treatment of adult patients with previously treated, advanced/metastatic or surgically unresectable cholangiocarcinoma with an FGFR2 rearrangement or fusion.”

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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<sup>1</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

If you have any questions, call me at 301-796-4803.

Sincerely,

*{See appended electronic signature page}*

Stacie Woods, Pharm.D.  
Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology  
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes





## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** Thursday, August 8, 2019, 2:00 PM – 3:00 PM, EDT  
**Meeting Location:** Teleconference

**Application Number:** 138179  
**Product Name:** pemigatinib (INCB054828)

**Indication:** For the treatment of adult patients with previously treated, advanced/metastatic or surgically unresectable cholangiocarcinoma with an FGFR2 rearrangement or fusion.

**Sponsor Name:** Incyte Corporation

**Meeting Chair:** Martha Donoghue, M.D.  
**Meeting Recorder:** Stacie Woods

### FDA ATTENDEES

Patricia Keegan, M.D., Division Director, OHOP/DOP2  
Naomi Horiba, M.D., Clinical Reviewer, OHOP/DOP2  
Martha Donoghue, M.D., Clinical Team Lead, OHOP/DOP2  
Whitney Helms, Ph.D., Nonclinical Team Lead, OHOP/DHOT  
Edwin Chow, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPV  
Sirisha Mushti, Ph.D., Statistician, OB/DBV  
Caryl Giuliano, Ph.D., CDRH  
Stacie Woods, Pharm.D., Regulatory Health Project Manager, OHOP/DOP2  
Mimi Biabile, M.S., Lead Regulatory Health Project Manager, OHOP/DOP2

### SPONSOR ATTENDEES

#### Incyte:

Ekaterine Asatiani, M.D., Regional Vice President, Drug Development  
Timothy C. Burn, Ph.D., Vice President, Bioinformatics and Molecular Diagnostics, Translational Sciences  
Luis Féliz, M.D., Medical Director, Clinical Development  
Tao Ji, Ph.D., Principle Investigator Clinical Pharmacokinetics  
Peter Langmuir, M.D., Group Vice President, Oncology Targeted Therapeutics  
Christine Lihou, Senior Director, Clinical Research Scientist  
Aaron Packman, MBA, Senior Director, Global Regulatory Affairs  
Gaurang Patel, M.D., Executive Medical Director, Head Global Risk Management & Safety Surveillance

Alan Roberts, Ph.D., Vice President, Toxicology  
Jean Surian, Ph.D., Associate Director, Global Regulatory Affairs  
Greg Taylor, Pharm.D., Vice President, Global Regulatory Affairs  
Huiling Zhen, Ph.D., Associate Director Biostatistics

**Foundation Medicine, Inc.:**

Coren Milbury, Ph.D., Director, Development Operations  
Christine Cappa, M.S., Senior Regulatory Affairs Specialist

**BACKGROUND**

On June 6, 2019, Incyte Corporation (Incyte) submitted a Type B, Pre-NDA meeting request to obtain FDA feedback on a planned NDA submission for accelerated approval of pemigatinib, primarily based upon top-line results from Study INCB 54828-202, for the proposed indication:

For the treatment of adult patients with previously treated, advanced/metastatic or surgically unresectable cholangiocarcinoma with an FGFR2 rearrangement or fusion.

Incyte Corporation (Incyte) submitted the meeting background package on July 1, 2019.

**Regulatory History**

- On October 27, 2014, the initial IND for INCB054828 (IND 124358) was submitted to the Division of Oncology Products 1 (DOP1). The IND contained the clinical protocol for Study INCB 54828-101 entitled, "A Phase 1, Open-label, Dose-escalation, Safety and Tolerability Study of INCB054828 in Subjects with Advanced Malignancies" and was allowed to proceed on November 26, 2014.
- On July 22, 2016, IND 131608 was submitted to the Division of Hematology Products. The IND included Protocol INCB 54828-203, entitled, "A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement." The study may proceed letter was issued on August 18, 2016.
- On January 25, 2018, Incyte submitted an end-of-phase 2 (EOP2) Chemistry, Manufacturing and Controls (CMC) only meeting request to discuss the CMC development plan for INCB054828 in support of pivotal clinical studies. The meeting was held on April 5, 2018.
- On January 30, 2018, IND 138179 was submitted to DOP2. The IND contained Protocol INCB 54828-202, entitled, "A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including

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FGFR2 Translocations Who Failed Previous Therapy.” A 30-day IND review waiver was granted.

- On March 12, 2018, FDA granted orphan drug designation to INCB054828 for the treatment of cholangiocarcinoma.
- On March 20, 2018, Incyte submitted an EOP2 meeting request to DOP2 to discuss an unplanned interim analysis of Study INCB 54828-202, based on the first 45 of the planned 100 patients, and to obtain feedback regarding a proposed design for Study INCB 54828-302 which is intended to verify the clinical benefit of INCB054828, assuming the drug is approved under the provisions of 21 CFR 314 Subpart H based on the results of Study INCB 54828-202 for the proposed indication of the “treatment of patients with previously treated unresectable cholangiocarcinoma with an FGFR2 fusion.” On March 22, 2018, FDA advised Incyte that the EOP2 meeting would only address questions regarding the proposed trial, Study INCB 54828-302, and that a separate Type C meeting should be requested to address questions regarding the non-clinical and clinical pharmacology programs to support an NDA in the setting of previously treated cholangiocarcinoma.
- On May 10, 2018, the Type B/EOP2 meeting on March 20, 2018, was cancelled by Incyte based on receipt of FDA’s Preliminary Meeting Comments, issued on May 8, 2018. In these responses, the following key advice was provided:
  - Regarding the proposed patient population in Study INCB 54828-302, FDA did not object to treatment of patients with INCB054828 in the first-line setting provided that patients are adequately consented about the availability of therapy that has been shown to prolong survival. However, the primary analysis population should be limited to those identified using an analytically validated assay for FGFR2 rearrangements. Therefore, FDA strongly recommended that the trial not be initiated until the analytically validated assay to be marketed as a companion diagnostic test with INCB054828 is available for use at clinical sites for patient selection.
  - Regarding Incyte’s proposed primary endpoint of progression-free survival (PFS) for Study INCB 54828-302, FDA stated that because overall survival (OS) is a direct measure of clinical benefit and because radiographic findings on liver and biliary tract imaging may be difficult to interpret, OS is the preferred regulatory endpoint to support approval in patients with unresectable and/or metastatic cholangiocarcinoma. FDA also stated that it is unlikely that the targeted magnitude of improvement in median PFS of 3.4 months will be of sufficient magnitude to verify and confirm the clinical benefit of INCB054828.
  - Regarding the proposed comparator arm of gemcitabine/cisplatin, FDA did not have objections; however, FDA stated that in order for results to be relevant to

the U.S. population, dose modification instructions in the protocol should be consistent with U.S. standard of care.

- FDA stated that the proposal to permit patients in the control arm to crossover to INCB054828 at the time of investigator-assessed disease progression in Study INCB 54828-302 may confound the ability to detect an overall survival benefit.
- Regarding the proposed statistical analyses, FDA agreed with Incyte's proposed analysis methods for primary (PFS) and the secondary efficacy endpoints (ORR and OS); but recommended the following changes:
  - Removal of the plan for stopping the trial early for efficacy based on the interim analysis result of PFS because the estimation of treatment effect may not be robust and reliable based on 35% of information.
  - Using O'Brien-Fleming spending function to determine alpha allocation for the interim analysis and final analysis based on the actual information fraction.
- On May 21, 2018, Final Written Responses were issued to Incyte in response to a Type C meeting request made on March 26, 2018. In these responses, the following key advice was provided:
  - Regarding the ability of a clinical data package to support an NDA, FDA stated that the available results of the unplanned post-hoc interim analysis of Study INCB 54828-202 were not sufficient to support an NDA. FDA recommended a minimum sample size of 100 patients with sufficient follow-up to adequately characterize safety and effectiveness of INCB054828 in patients with previously treated, unresectable cholangiocarcinoma with an FGFR2 fusion. FDA stated that in general, an ORR with a lower bound of the 95% confidence interval that is greater than 15%, accompanied by durations of response of sufficient magnitude to be considered clinically meaningful (e.g., at least 6 months in the majority of responders), and a favorable risk/benefit profile may provide sufficient evidence to support a marketing application seeking accelerated approval in the proposed patient population. FDA cautioned that ORR should be calculated using a denominator comprising all patients who received at least one dose of INCB054828 (as opposed to the "evaluable population") and duration of response should be calculated using the observed duration of response for each patient instead of Kaplan-Meier estimates, unless the data for duration of response are mature. FDA recommended that data be sufficiently mature to assess duration of response for a minimum of 12 months from the time of first onset of response for each responder. FDA also recommended that Incyte request a pre-NDA meeting to discuss adequacy of the data to support filing of a marketing application when top-level results meeting the criteria described above were available.

- Regarding the adequacy of the nonclinical toxicology and safety pharmacology studies to support an NDA submission, FDA stated that the finalized study report of the preliminary embryofetal development (EFD) study in rats mentioned in the meeting package, demonstrating clear positive results, may potentially be sufficient to support a marketing application; however, there was insufficient information on the study design for FDA to comment further. FDA also advised that if the preliminary rat EFD study was negative, study reports from definitive EFD studies in two species should be submitted in the NDA if available at the time of the NDA submission.
- Regarding the clinical pharmacology plan in support of an NDA, FDA advised Incyte to include in the NDA submission population PK and exposure-response analyses for safety and efficacy for all studies intended to support the NDA for INCB054828 in the proposed indication. FDA also encouraged Incyte to submit the study reports for the proposed renal and hepatic impairment studies in the NDA, if these reports were complete at the time of the planned NDA submission. Regarding Incyte's plan to submit ECG data from study INCB 54828-101 as well as the final analysis of concentration-QTc data in the NDA, FDA reiterated that Incyte should submit these data to the current IND for further FDA feedback on adequacy of the data and analysis in assessing the QT risk for INCB054828.
- On August 14, 2018, Incyte submitted Protocol INCB 54828-302 to IND 138179. This protocol retained PFS as the primary endpoint and the provision to permit crossover of patients from the control arm to the pemigatinib arm upon disease progression.
- On February 13, 2019, FDA granted breakthrough designation to pemigatinib for the treatment of patients with previously treated advanced/metastatic or unresectable cholangiocarcinoma with an FGFR2 fusion based on results of an interim analysis of Study INCB 54828-202.
- On March 15, 2019, Incyte requested a Type C, guidance meeting to discuss the content and format of an anticipated New Drug Application for pemigatinib (INCB054828) based on data derived from Study INCB 54828-202, entitled "A Phase 2 Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy." After review of the issues that needed discussion, and based on the statement of purpose, objectives, and proposed agenda, FDA granted this meeting as a Type B, initial Breakthrough Therapy Designation (iBTD) meeting. This meeting was held on June 12, 2019.

On June 14, 2019, FDA issued the Final Meeting Minutes letter and the following key points were included:

- FDA agreed with the proposal not to pool data from Study INCB54828-202 with the data obtained in patients with FGFR2-fusion-positive CCA in Studies INCB54828-101 and INCB54828-102, however the data from all three studies should be presented side by side in the SCE.
- FDA stated the proposed pooling strategy and planned safety analyses for the SCS and ISS appear reasonable.
- FDA agreed with Incyte's plan to provide the Case Report Forms (CRFs) as required in 21 CFR 314.50 and to also include CRFs for patients who had a serious adverse event while enrolled in the clinical trials included in the NDA.
- FDA agreed with the proposal to submit a safety update, however given that the submission would be reviewed under the provisions of accelerated approval, the safety update should be submitted 90 days after the original NDA submission. Additionally, the actual data cut-off date should be timed based on the date of the actual NDA submission.
- Regarding the efficacy update, only new information for the duration of follow up in responders identified in the initial NDA submission should be included. No new information regarding responses or confirmed responses observed between the data cutoff-dates for the initial submission and the efficacy update should be included.
- On April 25, 2019, Incyte requested a Type B, Pre-NDA, Chemistry, Manufacturing, and Controls, (CMC) only meeting. The meeting was held on June 18, 2019. On June 25, 2019, FDA issued the Final Meeting Minutes letter and the following key points were included:
  - FDA recommended the use of HPLC to address unspecified impurities, which may not be detected by NMR. Incyte agreed to utilize high-performance liquid chromatography (HPLC) for impurities in addition to nuclear magnetic resonance (NMR) for assay for both starting materials. FDA found this proposal acceptable.
  - FDA agreed that primary stability batches manufactured using starting material (b) (4) manufactured using Process A (the former process for (b) (4) as opposed to Process B) are acceptable.
  - FDA found Incyte's approach of developing the in vitro dissolution method appears reasonable. FDA provided the following recommendations:
    - Include the 20 minutes sampling time in the dissolution testing to characterize the entire dissolution profiles of the proposed drug products in all tested media (e.g., 0.01 N HCl, 0.1 N HCl, pH 4.5 and pH 6.8 dissolution media);



- Collect complete dissolution profiles (e.g., 10, 15, 20, 30, 45 and 60 minutes, until a plateau in the dissolution curve is reached) for primary registration batches throughout the stability program;
- Incyte's approach to normalize the dissolution data to reduce the impact observed differences in potency is not acceptable. FDA reminded Incyte that the dissolution profile should be complete and cover at least <sup>(b) (4)</sup> % of drug release of the label amount.
- FDA recommended that Incyte provide complete dissolution and PK linearity information in NDA to support the biowaiver request for the 9 mg and 13.5 mg tablets.

FDA stated that although the newly submitted information via email on 6/14/19, on appeared to show PK linearity between 9 and 20 mg, there are concerns at the lower doses, e.g., the inadequate subjects in the 1, 2, 4 and 6 mg dose groups in Study INCB54882-101. FDA recommended the "Bracketing Approach" for the proposed three strengths of Pemigatinib Tablets, by (i) conducting the acceptable BA/BE study using the highest and lowest strengths product, which are 13.5 mg and 4.5 mg tablets, (ii) requesting biowaiver for the middle strength tablets (9 mg), if all three strengths tablets are compositionally proportional and have the same dosage form, same drug release mechanism and manufacturing process, (iii) conducting multi-media comparative dissolution for all proposed strengths tablets.

FDA stated that we would review the study report supporting PK linearity submitted to the IND (including a brief description of the study design, the formulations used in the study, and the PK results) and will provide feedback within 30 days if there are any significant issues. FDA also re-iterated that the biowaiver will be reviewed during the NDA review period.

- Regarding the content and format of the CMC information to be included in the NDA, FDA stated submitting stability data in tabular format is acceptable, and to also provide a summary table that provides a concise view of all stability data. Regarding analytical procedures and validation, FDA stated Incyte may submit method summaries and validation report summaries, however, complete analytical procedures and validation reports should be available in the NDA.

### **Nonclinical**

INCB054828 is a small molecule inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases. Incyte has conducted repeat dose toxicology studies of up to 3-months duration in monkeys and rats, a full battery of genotoxicity studies, a phototoxicity assay, and several in vitro and in vivo pharmacology studies. A preliminary embryofetal development (EFD) study in rats

yielded a positive result (under IND 124358), thus Incyte will not conduct further EFD assessment.

## Clinical

### *Study INCB 54828-202*

Study INCB 54828-202, entitled “A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy”, is the study intended to support an NDA submission. Study INCB 54828-202 is an open-label single-arm study of INCB054828 in patients with advanced/metastatic or surgically unresectable cholangiocarcinoma whose tumors have progressed on at least one prior systemic therapy and harbor one of the following based on local genomic testing or central pre-screening and confirmed centrally:

- FGFR2 translocations with documented fusion partner by central testing (Cohort A, n=100),
- other FGF/FGFR alterations (Cohort B, n=20), or
- no FGF/FGFR alterations (Cohort C, n=20).

In Study INCB 54828-202, patients received pemigatinib 13.5 mg orally once daily for 14 days of each 21-day cycle until occurrence of disease progression, unacceptable toxicity related to treatment, or until another stopping criterion was met. Efficacy assessments were performed every 6 weeks for 4 cycles then every 9 weeks. The primary endpoint is ORR in Cohort A as assessed by a central independent review committee (IRC) according to RECIST 1.1. With the assumed rates of 33% for the intervention, a sample size of approximately 100 subjects would provide > 95% probability to have a 95% confidence interval with lower limit of > 15% assuming 10% lost to follow-up. Secondary endpoints are ORR in Cohort B, ORR in Cohort C, ORR in Cohorts A and B, PFS, DOR, disease control rate, and OS, characterization of safety and pharmacokinetics (PK).

### *Results*

At the time of the data cut on March 22, 2019 for Study INCB 54828-202, a total of 146 patients had been enrolled: 107 patients in Cohort A, 20 patients in Cohort B, and 18 patients in Cohort C. Of the patients enrolled in Cohort A, 31/107 (29%) were still on treatment at the time of the data cut. The most common reasons for treatment discontinuation among all patients enrolled in INCB 54828-202 study were progressive disease (58%), withdrawal by patient (6%), and adverse event (5.5%). In Cohort A, 96/107 (90%) were from the U.S. or Western Europe. The number of prior regimens (including chemotherapy, radiation, and surgery) was one for 65/107 (61%), two for 29/107 (27%), and three or more for 13/107 (12%) of patients in Cohort A.

A total of 38 confirmed responses among 107 patients were observed: 3 were complete and 35 were partial for an overall response rate (ORR) of 35.5% (95%CI: 26.5, 45.4) as assessed by IRC. All 3 complete responders and 12 of the partial responders had



ongoing responses at the time of the data cut, with a range of duration from 4.2 to 14.6 months. Based on the swimmer plot provided on Pages 15-18 of the meeting package, FDA estimates that 23/38 (61%) of responders had a duration of response of  $\geq 6$  months and 10/38 (26%) had a duration of  $\geq 12$  months. Thirty-five (35) of the 38 confirmed responders (92%) had at least 6 months of follow up from the time of initial response. There were no responses in Cohort B or C.

Most patients (92%) in the safety population (Cohorts A, B, and C) had at least one treatment emergent adverse event (TEAE) *that was considered related to study drug by the investigator [emphasis added]*. Grade 3 or higher “drug-related” TEAEs occurred in 64% of patients. Serious “drug-related” TEAEs occurred in 45% of patients, including 6 participants (4.1%) who had serious TEAEs with a fatal outcome. Study drug was interrupted in 43% of participants due to a TEAE. Overall, 9% of patients had TEAEs leading to discontinuation of pemigatinib.

The most common “drug-related” TEAEs occurring in more than 30% of patients were hyperphosphatemia (58%), alopecia (49%), diarrhea (47%), fatigue (43%), dysgeusia (40%), nausea (40%), constipation (35%), stomatitis (35%), dry mouth (34%) and decreased appetite (33%). The most common  $\geq$  Grade 3 TEAEs occurring in more than 3% of patients were hypophosphatemia (12%), arthralgia (6%), hyponatremia (5.5%), stomatitis (5.5%), abdominal pain (4.8%), fatigue (4.8%), hypotension (4.1%), palmar-plantar erythrodysesthesia (4.1%), anemia (3.4%), blood alkaline phosphatase increased (3.4%), and dehydration (3.4%).

In Cohort A, the following TEAEs observed at  $> 25\%$  higher incidence than in Cohort B or C were: alopecia, diarrhea, dysgeusia, constipation, dry mouth, dry eye, vomiting, and dry skin. The difference between cohorts is likely due to longer duration of exposure.

Serous retinal detachment was reported in 5 patients (3.4%). Two were Grade 1-2 and one was a Grade 3 serious adverse event (SAE).

## **CONTENT AND FORMAT OF PROPOSED NDA**

### *Chemistry, Manufacturing, and Controls*

The contents of the Quality portion of the NDA were discussed during the June 18, 2019, meeting, with discussion summarized in the minutes issued June 25, 2019.

### *Non-clinical Pharmacology/Toxicology*

The contents of the Non-Clinical portion of the NDA were addressed in the Written Responses Minutes issued May 21, 2018. Specifically, the NDA will contain study reports for repeat dose toxicology studies of up to 3-months duration in monkeys and rats, a full battery of genotoxicity studies, a phototoxicity assay, and several in vitro and in vivo pharmacology studies, and the preliminary EFD study in rats.

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[www.fda.gov](http://www.fda.gov)

*Clinical Pharmacology*

Incyte discussed the overview of the planned clinical pharmacology package of pemigatinib for the planned NDA in the teleconference held on April 12, 2019, which is listed in Table 1. Incyte will submit the pharmacokinetic (PK) report of food effect in the sub-cohort of Study INCB 5428-101 and the population PK report analysis, using pooled data from 3 clinical studies to evaluate the effect of organ impairment on pemigatinib PK, in the initial NDA submission. In addition, Incyte will submit the PBPK modeling report on the effect of P-gp and OCT2 inhibition on pemigatinib PK and the assessment of time course changes in creatinine and pemigatinib exposure. Incyte notes that a request for a Thorough QTc study waiver has been submitted to IND124358 (SDN0105) on June 5, 2019. FDA stated that the planned clinical pharmacology package generally appears to be acceptable for the filing of the planned NDA. However, the effect of pH evaluating agents on pemigatinib PK was not discussed in the meeting package.

**Table 1:**  
**Clinical Pharmacology Studies for Pemigatinib**

Study Number	Objective(s) of the Study	Study Treatment(s), Regimen, and Route of Administration	Planned Number of Participants, Age, and Sex	Healthy Participants or Diagnosis	Exposure	Study Report Inclusion in NDA
INCB 54828-104	To assess the effect of itraconazole and rifampin on INCB054828 pharmacokinetics when administered orally to healthy subjects	Cohort 1: Pemigatinib 4.5 mg on day 1 (fasted); itraconazole 200 mg QD on days 4-7 and 9-11 (fed); pemigatinib 4.5 mg and itraconazole 200 mg single dose on day 8 (fasted). Cohort 2: Pemigatinib 13.5 mg on day 1 (fasted); rifampin 600 mg on days 4-10 and 12 (fasted); pemigatinib 13.5 mg and rifampin 600 mg single dose on day 11 (fasted)	36, age 18 to 55 yrs, men and women	Healthy Participants	36 exposed	Yes
INCB 54828-105	To assess the mass Balance, pharmacokinetics, and metabolite profiles of a single oral dose of [ <sup>14</sup> C]INCB054828	Pemigatinib 11 mg +250 $\mu$ Ci [ <sup>14</sup> C]INCB054828 oral solution	7, age 18 to 55 yrs, men	Healthy Participants	7 exposed	Yes
INCB 54828-106	To assess the effect of esomeprazole and ranitidine on INCB054828 pharmacokinetics when administered orally in healthy subjects	Cohort 1: Pemigatinib 13.5 mg on day 1 (fasted); esomeprazole 40 mg QD on days 3-7 (fed); pemigatinib 13.5 mg and esomeprazole 40 mg on day 8 (fasted). Cohort 2: Pemigatinib 13.5 mg on day 1 (fasted); ranitidine 150 mg Q12h on days 3-5 (fed); pemigatinib 13.5 mg and ranitidine 150 mg Q12h on day 6 (fasted)	36, age 18 to 55 yrs, men and women	Healthy Participants	35 exposed	Yes
INCB 54828-107	To evaluate the pharmacokinetics and safety of pemigatinib in participants with normal hepatic function and participants with hepatic impairment	Pemigatinib 9 mg single dose	40, age 18 to 80 yrs., men and women	Healthy participants and participants with mild, moderate and severe hepatic impairment	5 exposed	No

*Clinical*

The content and format of the clinical sections of the planned NDA were discussed during the June 12, 2019, Initial Multidisciplinary Breakthrough Therapy Meeting and summarized in the minutes issued June 14, 2019.

Based on a data cut of March 22, 2019 for Study INCB 54828-202, Incyte will provide a minimum of 7 months' follow-up for all subjects in the efficacy analysis set. This will also include a minimum of 6 months' follow-up from the time of initial response for 35/38 (92%) currently known confirmed responders (the last responder achieved first response on October 16, 2018). At the time of the 4-month safety update, Incyte intends to provide a minimum of 12 months' overall follow-up for all subjects in the efficacy analysis set including a minimum of 6 months' follow-up from the time of initial response for all confirmed responders.

This application will be supported by efficacy from Studies INCB 54828-202, INCB 54828-201, and INCB 54828-203 and safety data from Studies INCB 54828-101, INCB 54828-102, INCB 54828-202, INCB 54828-201, and INCB 54828-203, with data cut-off dates of January or February 2019 for studies other than INCB 54828-202. The safety database will be limited to patients who received pemigatinib as a single agent (116, 25, 172, 146, 15) and presented in two pooled datasets

- The cholangiocarcinoma population consists of all patients with cholangiocarcinoma in Studies 101, 102, or 202 who received at least 1 dose of pemigatinib as a single agent.
- The all cancer population consists of patients with any cancer enrolled in Studies 101, 102, 201, 202, or 203 who have been treated with a least 1 dose of pemigatinib as a single agent.

FDA sent Preliminary Comments to Incyte on August 6, 2019.

**SPONSOR QUESTIONS AND FDA RESPONSES**

1. Overall, pemigatinib continues to be well tolerated, and the benefit risk supports use in the intended indication. Does the Agency agree that the top-line data for Study INCB 54828-202 supports an NDA submission for the proposed indication?

**FDA Response:** The proposed data package could support the filing of an NDA under the provisions of accelerated approval (21 CFR 314 Subpart H) for a proposed indication for the treatment of adult patients with previously treated, advanced/metastatic or surgically unresectable cholangiocarcinoma with an FGFR2 fusion, as detected by an FDA-approved test. As stated in the initial Breakthrough Therapy Designation meeting on June 12, 2019, FDA does not agree that the design of Study INCB 54828-202 is adequate to support the filing of an application seeking regular approval nor that the application would support accelerated approval for the treatment of patients with previously treated,

advanced/metastatic or surgically unresectable cholangiocarcinoma with an FGFR2 rearrangement.

At the meeting on June 12, 2019, FDA requested that the meeting package for this pre-NDA meeting include results of the bridging study and the analytical accuracy study discussed with CDRH. Please indicate when the result of these studies will be submitted to the pre-submission in order to allow CDRH to reach agreement on the content of the planned PMA supplement for the companion diagnostic test.

**Incyte's response received via email on August 7, 2019:** The Sponsor would like to further clarify this response from the Division.

Foundation Medicine, Inc. (FMI) intends that the clinical bridging study report will be included in the sPMA submission submitted in late Oct. 2019. The analytical concordance study report, including the increased negative samples requested by FDA, will be submitted as a supplement to the sPMA submission. FMI anticipates submitting this supplement in Dec. 2019.

**Discussion during the August 8, 2019 meeting:**

Incyte requested clarification regarding FDA's restatement of the indication that referenced only patients with FGFR2 fusion-positive cholangiocarcinoma and not those with FGFR2 rearrangements. In response to FDA's query, Incyte stated that 15 of the 107 patients in Cohort A had cholangiocarcinoma with an FGFR2 rearrangement; 6 of those 15 patients were identified by the BICR as having an objective response. FDA stated that the clinical experience in patients with cholangiocarcinoma with an FGFR2 rearrangements was very limited. If Incyte seeks to include this population, Incyte should justify this request based on nonclinical data (in vitro data demonstrating similar inhibition at clinical achievable exposures) and clinical data supporting extrapolation of results from patients with FGFR2 fusion-positive tumors, including similarity of the natural history of the disease.

## ADDITIONAL COMMENTS

### CMC

2. Confirm that the planned NDA will address all of FDA's comments and recommendations provided in the minutes for the June 18, 2019, Pre-NDA CMC meeting.

**Incyte's response received via email on August 7, 2019:** Incyte confirms that the planned NDA will address all of FDA's comments and recommendations

provided in the minutes for the June 18, 2019, Pre-NDA CMC meeting. No further discussion is required by the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

### *Clinical Pharmacology*

3. Prior to the August 8, 2019, meeting, provide the plan for assessing the effect of a proton pump inhibitor on the pharmacokinetics of pemigatinib. These data should be provided in Module 5 of the planned NDA or a justification for not providing this data should be provided in the Summary of the Clinical Pharmacology.

**Incyte's response received via email on August 7, 2019:** In order to assess the effect of a proton pump inhibitor on the pharmacokinetics of pemigatinib, the following clinical pharmacology study was conducted:

- INCB 54828-106: An Open-Label Study to Assess the Effect of Esomeprazole and Ranitidine on INCB054828 Pharmacokinetics When Administered Orally in Healthy Participants (submitted to IND 124,358; February 13, 2018; Serial No. 0072)

The final clinical study report will be included in Module 5 of the planned NDA.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

4. FDA refers to the July 29, 2019 email regarding the proposal for addressing effects of pemigatinib on the QT interval, in which FDA stated "PK/ECG data from study INCB 54828-101 is adequate to characterize the effect of pemigatinib on the QTc interval at the 13.5 mg QD dose level. The data suggests a lack of large mean effect (i.e., >20 ms) at the 13.5 mg QD dose level. We agree that a dedicated QT study is not needed for the 13.5 mg QD dose."

**Incyte's response received via email on August 7, 2019:** Incyte acknowledges this comment. No further discussion is required from the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

*Clinical*

5. Confirm that the planned NDA will address all of FDA's comments and recommendations provided in the minutes for the June 12, 2019, Type B, initial interdisciplinary BTM meeting.

**Incyte's response received via email on August 7, 2019:** Incyte confirms that the planned NDA will address all of FDA's comments and recommendations provided in the minutes for the June 12, 2019, Type B, initial interdisciplinary BTM meeting. No further discussion is required from the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

6. Based on the meeting package, FDA expects that no REMS or other minor components will be submitted in the NDA. Confirm that no REMS will be submitted in the NDA, and no minor application components will be submitted within 30 calendar days after the submission of the NDA.

**Incyte's response received via email on August 7, 2019:** Incyte confirms that no REMS will be submitted in the NDA, and no minor application components will be submitted within 30 calendar days after the submission of the NDA. No further discussion is required from the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

7. As stated in the June 12, 2019 Type B meeting, only new information for the duration of follow up in responders identified in the initial NDA submission should be included in the efficacy update. No new information regarding responses or confirmed responses observed between the data cutoff dates for the initial submission and the efficacy update should be included.

**Incyte's response received via email on August 7, 2019:** Incyte acknowledges this comment from the Division. No further discussion is required from the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

8. Please clarify if the sPMA for the FoundationOne CDx will be submitted at the same time as the NDA for pemigatinib.

**Incyte's response received via email on August 7, 2019:** Foundation Medicine Inc. (FMI) plans to submit the sPMA for the FoundationOne CDx within 30 days of the submission of the NDA for pemigatinib. The pemigatinib NDA submission



is targeted for September 30, 2019. No further discussion is required from the Sponsor.

**Discussion during the August 8, 2019 meeting:** No discussion occurred.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed during this meeting and in the June 18, 2019, CMC only Pre-NDA meeting as well as the June 12, 2019, iBTD meeting. Agreements reached are documented in the minutes for these meetings.
- Incyte confirmed that Modules 1 and 3 of the NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities that are included or referenced in the application.
- A preliminary discussion was held on the need for risk evaluation and mitigation strategies (REMS). FDA agreed that Incyte was not required to submit a REMS in order for the application to be filed. A final determination regarding the need for REMS will be made during review of the application.
- Incyte did not submit a proposal for a Formal Communication Plan in the pre-meeting package, therefore FDA stated that communications during review will include a Mid-cycle communication and Late-cycle meeting as well as information requests as needed. At this time, FDA does not recommend that an application orientation meeting be held but will make a final determination upon receipt of the NDA.
- Incyte stated that they will submit a complete application and therefore, there are no agreements for late submission of application components.

## **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Since INCB054828 has orphan designation for the treatment of cholangiocarcinoma, you are exempt from these requirements provided the NDA is submitted prior to August 18, 2020. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application.

However, please be aware that Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting and no later than 210 days prior to submission of an NDA if that NDA is to be submitted **after** August 18, 2020. The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.<sup>2</sup>

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<sup>2</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>  
U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)



## **FDARA REQUIREMENTS**

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants<sup>3</sup> to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at [OCEPERC@fda.hhs.gov](mailto:OCEPERC@fda.hhs.gov). For further guidance on pediatric product development, please refer to FDA.gov.<sup>4</sup>

## **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information<sup>5</sup> and Pregnancy and Lactation Labeling Final Rule<sup>6</sup> websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

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<sup>3</sup> See the guidance for industry "*Formal Meetings Between the FDA and Sponsors or Applicants.*"

<sup>4</sup> <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

<sup>5</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

<sup>6</sup> <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

### **DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length,

- randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
  - Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

### **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.<sup>7</sup>

### **MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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<sup>7</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

### **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.<sup>8</sup>

### **ONCOLOGY PILOT PROJECTS**

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review

<sup>8</sup> <https://www.fda.gov/media/85061/download>

process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR<sup>9</sup>: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.  
AssessmentAid<sup>10</sup>

#### **ISSUES REQUIRING FURTHER DISCUSSION**

None

#### **ACTION ITEMS**

None

#### **ATTACHMENTS AND HANDOUTS**

None

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<sup>9</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

<sup>10</sup> <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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STACIE A WOODS  
08/12/2019 08:55:43 AM

# CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	138179
Request Receipt Date	December 19, 2018
Product	Pemigatinib (INCB054828)
Indication	For the treatment of patients with previously treated advanced/metastatic or unresectable cholangiocarcinoma with an FGFR2 fusion
Drug Class/Mechanism of Action	Fibroblast growth factor receptor inhibitor (small molecule)
Sponsor	Incyte Corporation
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	February 17, 2019

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

## **Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.**

### **1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Pemigatinib is intended for the treatment of patients with previously treated advanced unresectable or metastatic cholangiocarcinoma with an FGFR2 fusion

### **2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

YES  NO

### **3. Was the BTDR submitted to a PIND?**

YES  NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

### **4. Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening<sup>1</sup>?

YES  NO

*If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>



- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
- Undetermined
- NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence
  - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
  - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
  - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
  - v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

**5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:**

*If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.*

*If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**6. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

- *Information regarding the disease and intended population for the proposed indication.*

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>



- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Pemigatinib is a small molecule inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases (FGFR1, FGFR2, and FGFR3). Fibroblast growth factor signaling contributes to cell proliferation, survival, migration, and angiogenesis, and is physiologically involved in skeletal development and tissue homeostasis. Alterations in genes (including mutations, amplifications, and translocations) encoding FGFRs can cause aberrant fibroblast growth factor pathway activation and tumorigenesis.

The estimated incidence of cholangiocarcinoma (CCA) (intrahepatic and extrahepatic) in the U.S. is approximately 5000/year (Bridgewater J., 2014). CCA generally occurs after the fourth decade of life, with the risk being slightly higher in men than women. The rising incidence has been linked with the increasing incidences of hepatitis C virus infection (Bergquist et al., 2015). Other risk factors specifically associated with intrahepatic CCA (iCCA) are hepatitis B virus infection and hepatolithiasis. However, in most patients with iCCA no putative risk factor(s) can be detected at the diagnosis. (Ebata et al., 2016).

Resection is the only potentially curative option for patients with CCA. However, as the disease typically becomes symptomatic only once it has progressed to a late stage, only a small minority of patients have resectable tumors at diagnosis (Ghouri et al., 2015). For patients with unresectable or metastatic tumors, the prognosis is dismal and the majority of patients die within a year of diagnosis. Based on the results of the ABC-02 trial, the standard of care for these patients is combination chemotherapy with gemcitabine and cisplatin. In this study, 410 patients with locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer were randomized to receive either cisplatin (25 mg/m<sup>2</sup>) in combination with gemcitabine (1000/m<sup>2</sup>) administered on Days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000/m<sup>2</sup> on Days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary endpoint was overall survival. After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; p=0.049) (Valle et al., 2011).

FGFR2 gene fusions have been observed in 13-14% of iCCA and are more common in younger patients and in females (Churi et al., 2014; Arai et al., 2014; Graham et al., 2014). In a retrospective analysis of 377 patients with CCA, 95 had FGFR genetic alterations. FGFR2 genetic alterations were most common (n = 74, with 63 fusions), and seen in iCCA. In patients with iCCA, FGFR genetic alterations occurred more frequently in younger patients ( $\leq 40$  years; 20%) compared with older patients ( $> 40$  years; 6.7%), presented at an earlier stage (TNM stage I/II vs. III/IV: 35.8% vs. 22%, respectively), and were associated with a longer survival (OS) compared with patients without FGFR genetic alterations (37 vs. 20 months respectively), even after exclusion of 36 patients treated with FGFR inhibitors. There was no OS difference between patients with CCA with FGFR2 fusions (n = 63) versus patients with CCA harboring other FGFR genetic alterations (n = 29). Median OS in 50 patients with FGFR genetic alterations who did not receive FGFR-directed therapy was 24.3 months (95% CI 18.2; 49.8) compared with 44.8 months (95% CI 24.5 to NR) in 36 patients who received FGFR-directed therapy.

## **8. Information related to endpoints used in the available clinical data:**

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

This BTDR is supported by confirmed overall response rate (ORR) per independent central review (ICR) using RECIST 1.1 criteria, which is the primary endpoint of Study INCB 54828-202. In general, the preferred efficacy endpoint in CCA is overall survival (OS) because it is a direct measure of clinical benefit and because tumor

burden can be difficult to assess radiologically in patients with CCA. In general, ORR or PFS of large magnitude can be considered reliable surrogates for OS.

In the ongoing randomized study of pemigatinib in the first-line setting, INCB 54828-302, intended to support a marketing application, the primary endpoint is progression-free survival (PFS). In the preliminary comments to a Type B meeting scheduled for May 14, 2018 that Incyte subsequently canceled, FDA advised Incyte that OS is the preferred regulatory endpoint to support approval in patients with unresectable or metastatic CCA, but that a robust improvement in PFS that is large in magnitude, statistically persuasive, and associated with an acceptable risk-benefit profile may support approval in the first-line setting.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
  - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
  - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Overall survival is the preferred endpoint for assessing efficacy of treatments for patients with metastatic or unresectable CCA. In general, PFS of large magnitude and ORR of large magnitude and duration can be considered reliable surrogates for OS.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

There are no other known outcome measures or biomarkers that the Division would consider likely to predict clinical benefit in patients with CCA.

9. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

The standard of care for systemic first-line treatment of CCA is the combination cisplatin/gemcitabine, based on demonstration of improved OS in patients randomized to cisplatin/gemcitabine vs. gemcitabine alone (see the answer to Question 7 for additional details). Although both drugs are approved for multiple cancers, neither are approved for the treatment of CCA. The National Comprehensive Cancer Network (NCCN, [https://www.nccn.org/professionals/physician\\_gls/pdf/hepatobiliary.pdf](https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf)) recommends clinical trials and fluoropyrimidine as second-line treatments. For patients with proven microsatellite instability-high (MSI-H) status, treatment with a checkpoint inhibitor is recommended. Pembrolizumab is approved for the treatment of patients with unresectable or metastatic MSI-H/dMMR solid tumors that have progressed following prior treatment. The

prescribing information shows that 11 patients had biliary cancer with an ORR of 27% (95% CI 6; 61) and a range in duration of response from 11.6+ to 19.6+ months.

A systematic literature review evaluated the evidence for use of second-line chemotherapy in a molecularly unselected population of patients with advanced biliary cancer who progressed on first-line therapy (Lamarca et al., 2014). The review included 761 subjects across 25 studies and showed a median PFS duration of 3.2 months (95% CI: 2.7 to 3.7), response rate of 7.7% (95% CI: 4.6 to 10.9), and a median OS duration of 7.2 months (95% CI: 6.2 to 8.2). The following table summarizes some of the studies included in the meta-analysis.

**Table 1. Select studies in Lamarca meta-analysis of patients with CCA treated in the second-line setting**

Treatment	Line	Study type	N pts	ORR (%)	mPFS (months)	mOS (months)
Gemcitabine	2 <sup>nd</sup> /3 <sup>rd</sup>	Retrospective	17	28.5	5.1	17
Fluoropyrimidine-based	2 <sup>nd</sup>	Retrospective	255	1.2	1.8	13.2
Gemcitabine-based	2 <sup>nd</sup>	Retrospective	29	0	6.1	6.5
Gemcitabine/cisplatin	2 <sup>nd</sup>	Retrospective	60	1.7	3.5	6.7
Everolimus	2 <sup>nd</sup>	Single arm, open label	39	5.1	3.2	7.7
Irinotecan	2 <sup>nd</sup>	RCT, open-label	30	6.7	2.4	7.3
Irinotecan	3 <sup>rd</sup> -4 <sup>th</sup>	Single-arm, open-label	13	7.7	1.8	6.7
5FU-cisplatin	2 <sup>nd</sup>	Retrospective	66	8.3	2.6	6.2
Sunitinib	2 <sup>nd</sup>	Single-arm, open-label	56	8.9	1.7	4.8
Capecitabine/irinotecan	2 <sup>nd</sup>	RCT, open-label	30	13.3	3.7	10.1
FOLFOX	2 <sup>nd</sup>	Single-arm, open-label	37	21.2	3.1	6.9
FOLFIRI/bevacizumab	2 <sup>nd</sup>	Retrospective	13	38.4	8	20

There are no published studies evaluating the efficacy of chemotherapy in patients with FGFR2-fusion CCA.

**10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

On December 13, 2018, (b) (4) QED Therapeutics submitted a BTDR for infigratinib (BGJ398) for the second-line treatment of advanced or metastatic CCA in patients with FGFR2 fusions. Infigratinib is an orally available FGFR tyrosine kinase inhibitor. In an interim analysis of 71 previously treated patients with iCCA and FGFR2 fusions, the ORR was 25.4% (95% CI: 15.8, 37.1) as assessed by the investigator. The median duration of response (DOR) was 4.42 months (9% CI: 3.71, 7.27) and 23.5% of responding patients had a duration of response greater than 6 months (DOR range: 1.51 months to 11.1 months).

**11. Information related to the preliminary clinical evidence:**

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design<sup>4</sup>, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

This BTDR is supported by an interim analysis of a data from Cohort A in Study INCB 54828-202, an open-label, activity estimating, study of pemigatinib in subjects with advanced unresectable or metastatic CCA with FGFR2 translocations (Cohort A), with other FGF/FGFR alterations (Cohort B), or who are negative for FGF/FGFR

<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

<sup>4</sup> Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

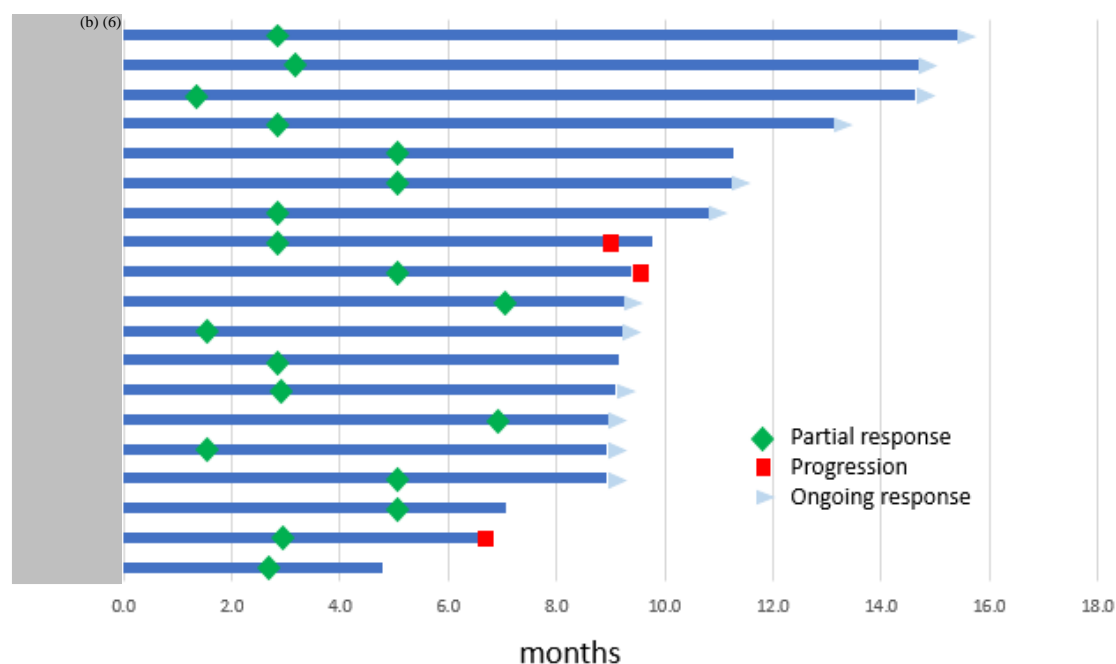
alterations (Cohort C). The data provided in the BTDR are based on a cutoff date of July 24, 2018. At the time of this BTDR submission, the trial completed enrollment in the US and EU, but was ongoing in Japan.

In Study INCB 54828-202, patients receive pemigatinib 13.5 mg orally once daily for 14 consecutive days of each 3-week cycle until occurrence of disease progression, unacceptable toxicity related to treatment, or until another stopping criterion is met. Efficacy assessments are performed every 6 weeks for 4 cycles then every 9 weeks. The primary endpoint is ORR in Cohort A as assessed by an independent review committee (IRC) according to RECIST 1.1. Secondary endpoints are ORR in Cohort B, ORR in Cohort C, ORR in Cohorts A and B, PFS, DOR, disease control rate, and OS, characterization of safety and pharmacokinetics (PK).

As of July 24, 2018, 91 patients had been enrolled and treated in Cohort A. This BTDR is supported by interim results from the first 47 patients who had been followed for at least 8 months following initiation of treatment as of the cutoff date. Non-Asian patients comprised 94% of the Cohort A population; most patients were 65 years of age or younger (79%) with a median age of 55 years in Cohort A vs. 63 years and 65 years in Cohorts B and C respectively. Female patients represented 53% of the population. Forty-nine percent (49%) of patients in Cohort A had received at least 2 prior chemotherapy regimens and all patients had received at least one prior therapy.

The confirmed ORR per RECIST 1.1 according to IRC assessment was 19/47 (40.4% [95% CI: 26.4, 55.7]); all responses were partial responses. The probability of maintaining response for at least 6 months was 86%, as assessed by Kaplan-Meier method. At the time of data cutoff, 12 responses were ongoing: 2.1+, 2.3+, 4+, 6.3+, 6.4+, 7.6+, 7.8+, 8.1+, 10.5+, 11.6+, 12.7+, and 13.4+ months. In 63% of responding patients the DOR was 6 months or longer. See Figure 1.

**Figure 1. Swimmer plot of 19 responding patients in Study INCB 54828-202 Responders**



Source: Reviewer table, data cutoff date: July 24, 2018

Among the 91 patients enrolled to Cohort A as of July 24, 2018, 79 were evaluable for response. The median follow-up period was 9.4 months (range 0.03 to 16.8 months). In the total evaluable population of 79 patients, 24 demonstrated confirmed partial response resulting in an ORR of 30% (95% CI: 21, 42).

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Of the 134 subjects included in the safety analysis, 97% reported at least one treatment-emergent adverse event (AE) and 87% had a treatment-related AE. Thirty-one percent (31%) of patients required a dose interruption and 5% required a dose reduction. The incidence of serious adverse events (SAEs) was 37%. Events leading to treatment reduction included stomatitis, asthenia, arthralgia, nail dystrophy, nail toxicity, onychomadesis and palmar-plantar erythrodysesthesia syndrome. Treatment was discontinued due to an AE in 9% of patients. Grade 3 and 4 AEs were reported in 51% of patients. Hyperphosphatemia, alopecia, diarrhea, fatigue, dry mouth, stomatitis, decreased appetite, constipation, nausea, and arthralgia, were AEs observed in  $\geq 20\%$  patients.

**12. Division's recommendation and rationale (pre-MPC review):**

GRANT :

Provide brief summary of rationale for granting:

The ORR of 40% (95% CI: 26.4, 55.7) observed with pemigatinib in the subgroup of 47 patients with previously treated iCCA with FGFR2 fusions who received treatment with pemigatinib and have been followed for at least 8 months following initiation of treatment with pemigatinib represents an improvement over available second-line chemotherapy, which has a reported ORR of 7.7% (95% CI: 4.6 to 10.9) based on a meta-analysis of unselected patients with CCA in the second-line setting and beyond. Furthermore, the duration of response observed with pemigatinib is clinically meaningful; the median duration of response has not been reached and 63% of responders had a DOR of 6 months or longer. Although the observed ORR among a larger subset of patients (n=79 evaluable for response) was lower (30%) than the ORR observed in the initial 47 patients, it appears that in some cases the time to response is long (up to 7 months) and additional responses may be seen with a longer duration of follow up in the larger patient subset. The adverse event profile observed with pemigatinib is acceptable in light of the serious nature and poor prognosis associated with iCCA.

*Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.*

DENY:

Provide brief summary of rationale for denial:

*Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:*

**13. Division's next steps and sponsor's plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

On November 17, 2018, Incyte submitted Study INCB 54828-302, entitled “A Phase 3, Open-Label, Randomized, Active-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 Versus Gemcitabine Plus Cisplatin Chemotherapy in First-Line Treatment of Participants With Unresectable or Metastatic Cholangiocarcinoma With FGFR2 Rearrangement” intended to support a marketing application. FDA provided preliminary comments in advance of an End of Phase 2 meeting to be held on May 14, 2018, which Incyte canceled, in which FDA advised that:

- The primary analysis population should be limited to those identified using an analytically validated assay for FGFR2 rearrangements.
- OS is the preferred regulatory endpoint, but a robust improvement in PFS that is large in magnitude, statistically persuasive, and associated with an acceptable risk-benefit profile may support approval in the first-line setting; however, it is unlikely that the targeted magnitude of improvement in median PFS of 3.4 months will be of sufficient magnitude to verify and confirm the clinical benefit of INCB054828.
- Incyte should remove the planned interim analysis and early stopping for efficacy.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

#### 14. List references, if any:

Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology*, 2014; 59(4): 1427-34.

Bergquist A, and von Seth E. Epidemiology of cholangiocarcinoma. *Best Practice & Research Clinical Gastroenterology*, 2015; 29(2): 221-232.

Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol*, 2014; 60(6): 1268-1289.

Churi CR, Shroff R, Wang Y, et al. Mutation Profiling in Cholangiocarcinoma: Prognostic and Therapeutic Implications. *PLoS One*, 2014; 9(12).

Ghouri YA, Mian I, and Blechacz B. Cancer Review: Cholangiocarcinoma. *J Carcinog*, 2015; 14(1).

Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. *Hum Pathol*, 2014; 45(8):1630-8.

Tyson GL and El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology*, 2011; 54(1): 173-184.

Valle J, Wasan H, Palmer DH, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. *N Engl J Med*, 2010; 364(14): 1273-1281.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES  NO

#### 16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation   
Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }  
Team Leader Signature: { See appended electronic signature page }  
Division Director Signature: { See appended electronic signature page }

**Revised 10/3/18/M. Raggio**

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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MARGIT N HORIBA  
02/12/2019 10:01:01 AM

MARTHA B DONOGHUE  
02/12/2019 01:57:54 PM

PATRICIA KEEGAN  
02/12/2019 03:02:04 PM





IND 138179

## MEETING PRELIMINARY COMMENTS

Incyte Corporation  
Attention: Aaron Packman, MBA  
Senior Director, Regulatory Affairs  
1801 Augustine Cut-Off  
Wilmington, DE 19803

Dear Mr. Packman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "INCB054828."

We also refer to your March 20, 2018, correspondence, received March 20, 2018, requesting a meeting to discuss the results of an unplanned interim analysis of the ongoing study, Protocol INCB 54828-202, entitled, "A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy," which is intended to support a new drug application (NDA), submitted under the provisions of 21 CFR 314 Subpart H (accelerated approval) for the proposed indication of "the treatment of previously treated, unresectable cholangiocarcinoma with an FGFR2 fusion." You also requested feedback on the design of the proposed Study INCB 54828-302, which is intended to verify the clinical benefit of INCB054828 for this indication.

We also refer to our March 22, 2018, telephone conversation and our Meeting Granted letter dated March 27, 2018, in which we advised you that the EOP2 meeting would only address questions regarding the proposed trial, Study INCB 54828-302 (questions 7-12) and that a separate Type C meeting be requested to address questions 1 through 6 regarding the non-clinical and clinical pharmacology programs to support an NDA in the setting of previously treated cholangiocarcinoma. Finally, we refer to our Meeting Granted letter April 6, 2018, stating that written responses to your questions regarding the nonclinical and clinical pharmacology programs to support an NDA will be provided by June 9, 2018.

Our preliminary responses to your meeting questions 7 through 12 as contained in your March 20, 2018, correspondence are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-4803.

Sincerely,

*{See appended electronic signature page}*

Stacie Woods, Pharm.D.  
Regulatory Health Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## PRELIMINARY MEETING COMMENTS

**Meeting Type:** B  
**Meeting Category:** End of Phase 2  
**Meeting Date and Time:** May 14, 2018, 3:00 – 4:00 PM EDT  
**Meeting Location:** White Oak Building 22, Room 1313  
**Application Number:** 138179  
**Product Name:** INCB054828  
**Indication:** Treatment of previously treated, unresectable cholangiocarcinoma with an FGFR2 fusion  
**Sponsor/Applicant Name:** Incyte Corporation

### FDA ATTENDEES (tentative)

Patricia Keegan, M.D., Division Director, DOP2  
Naomi Horiba, M.D., Clinical Reviewer, DOP2  
Martha Donoghue, M.D., Clinical Team Lead, DOP2  
Stephanie Aungst, Ph.D., Nonclinical Reviewer, DHOT  
Whitney Helms, Ph.D., Nonclinical Team Lead, DHOT  
Brain Furmanski, Ph.D., Clinical Pharmacology Reviewer, DCPV  
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead, DCPV  
Lisa Rodriguez, Ph.D., Statistician Team Lead, DBV  
Navid Homayouni, M.D., GCP Reviewer, OSI  
Janine Stewart, Pharm.D., Safety Evaluator, OSE  
Stacie Woods, Pharm.D., Regulatory Health Project Manager, DOP2  
Mimi Biable, M.S., Lead Regulatory Health Project Manager, DOP2

### SPONSOR ATTENDEES

Ekaterine Asatiani, M.D., Regional Vice President, Drug Development  
Timothy C. Burn, Ph.D., Vice President, Bioinformatics and Molecular Diagnostics, Translational Sciences  
Luis Féliz, M.D., Medical Director, Clinical Development  
Kevin Hou, Ph.D., Vice President Biostatistics & Programming  
Tao Ji, Ph.D., Principle Investigator Clinical Pharmacokinetics  
Peter Langmuir, M.D., Group Vice President, Oncology Targeted Therapeutics  
Christine Lihou, Senior Director, Clinical Research Scientist  
Aaron Packman, MBA, Senior Director, Regulatory Affairs  
Jean Surian, Ph.D., Senior Manager, Regulatory Affairs  
Huiling Zhen, Ph.D., Associate Director Biostatistics

**Introduction:**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 14, 2018, 3:00 – 4:00, PM, EST, at 10903 New Hampshire Avenue, White Oak Building 22, Conference Room 1313, Silver Spring, Maryland, between Incyte Corporation and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

**BACKGROUND**

On March 20, 2018, Incyte submitted a request for a Type B, End of Phase 2 (EOP2) meeting to discuss and obtain the Agency's feedback regarding a proposed design of Study INCB 54828-302, which is intended to verify the clinical benefit of INCB054828 and to discuss whether the preliminary clinical results of the ongoing Study INCB 54828-202, entitled, "A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy" could support a new drug application (NDA) under the provisions of 21 CFR 314 Subpart H (accelerated approval).

Incyte Corporation (Incyte) submitted the meeting package on April 2, 2018.

**Regulatory history**

- On October 27, 2014, the initial IND for INCB054828 (IND 124358) was submitted to the Division of Oncology Products 1 (DOP1). The IND included the clinical protocol for Study INCB 54828-101 entitled, "A Phase 1, Open-label, Dose-escalation, Safety and Tolerability Study of INCB054828 in Subjects with Advanced Malignancies" and became active on November 26, 2014.
- On July 22, 2016, IND 131608 was submitted to the Division of Hematology Products. The IND included Protocol INCB 54828-203, entitled, "A Phase 2, Open-Label, Monotherapy, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Myeloid/Lymphoid Neoplasms with FGFR1 Rearrangement." The study may proceed letter was issued on August 18, 2016.

- On January 25, 2018, Incyte submitted an end-of-phase 2 (EOP2) Chemistry, Manufacturing and Controls (CMC)-only meeting request to discuss the CMC development plan for INCB054828 in support of Phase 3 clinical studies. FDA's preliminary comments were issued on March 29, 2018. A teleconference was held on April 5, 2018. FDA's meeting minutes were issued on April 18, 2018.
- On January 30, 2018, IND 138179 was submitted to DOP2. The IND included Protocol INCB 54828-202, entitled, "A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects with Advanced/Metastatic or Surgically Unresectable Cholangiocarcinoma Including FGFR2 Translocations Who Failed Previous Therapy." A 30-day review waiver was granted for this IND.
- On March 12, 2018, FDA granted orphan drug designation for INCB054828 for the treatment of cholangiocarcinoma.
- Incyte submitted an EOP2 meeting request on March 20, 2018 to DOP2 to discuss an unplanned interim analysis of Study INCB 54828-202, based on the first 45 of the planned 100 patients, and to obtain feedback regarding a proposed design for Study INCB 54828-302 which is intended to verify the clinical benefit of INCB054828, assuming the drug is approved under the provisions of 21 CFR 314 Subpart H based on the results of Study INCB 54828-202 for the proposed indication of the "treatment of patients with previously treated, unresectable cholangiocarcinoma with an FGFR2 fusion." On March 22, 2018, FDA advised Incyte that the EOP2 meeting would only address questions regarding the proposed trial, Study INCB 54828-302. On April 6, 2018, FDA notified Incyte that written responses would be provided by June 9, 2018, to address questions regarding the non-clinical and clinical pharmacology programs intended to support a planned NDA for INCB054828 for the treatment of patients with previously treated cholangiocarcinoma.

## **Nonclinical**

INCB054828 is an inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases. The Sponsor has conducted acute (28-day) and chronic (3-month) repeat dose toxicology studies in cynomolgus monkeys and rats, a full genotoxicity profile, a phototoxicity assay, and several in vitro and in vivo pharmacology studies to support the proposed Phase 3 trial.

## Clinical and Statistics

### *INCB 54828-202*

Protocol INCB 54828-202 is an open-label single-arm study of INCB054828 in patients with advanced/metastatic or surgically unresectable cholangiocarcinoma whose tumors have progressed on at least one prior systemic therapy and harbor one of the following:

- FGFR2 translocations with known or likely fusion partners per next generation sequencing (NGS) (Cohort A, n=100),
- other FGF/FGFR alterations (Cohort B, n=20), or
- no FGF/FGFR alterations (Cohort C, n=20).

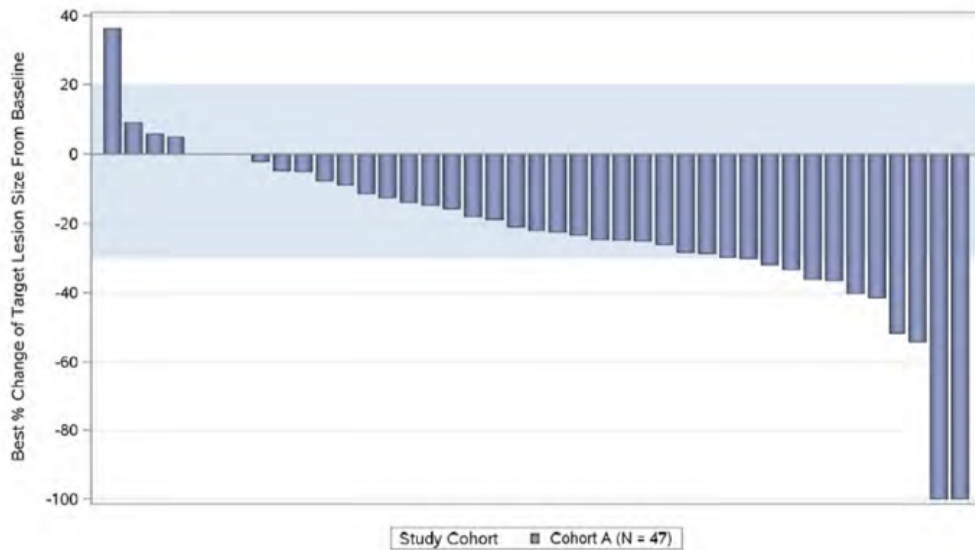
The primary endpoint is overall response rate (ORR) in Cohort A as assessed by an independent review committee (IRC) according to RECIST 1.1.

Patients receive INCB054828 13.5 mg orally daily on a 2-week-on and 1-week-off schedule until disease progression, toxicity related to treatment, or other stopping criterion is met. Efficacy assessments are performed every 6 weeks for 4 cycles then every 9 weeks.

As of March 14, 2018, a total of 87 patients have been treated in Study INCB 54828-202. Sixty-four (64) patients have been enrolled to Cohort A, 22 to Cohort B (enrollment complete), and 18 to Cohort C (enrollment complete). At the time of analysis (cutoff date November 27, 2017), 47 patients had enrolled in Cohort A with 45 patients evaluable for response. In Cohort A, 94% of patients had intrahepatic cholangiocarcinoma. The median number of prior chemotherapy regimens was 2 (range 1-5).

Incyte provided preliminary results showing that among 47 patients in Cohort A, 8 had a confirmed partial response (ORR 17%; 95% CI 7.6%, 31%) as assessed by IRC. An additional 3 patients had unconfirmed partial responses on scans performed just prior to the data cutoff. If confirmed, the ORR would be of 23% (95% CI: 12%, 38%). See Figure 1 for a waterfall plot of change of target lesion size from baseline in Cohort A as assessed by IRC in the efficacy evaluable population.

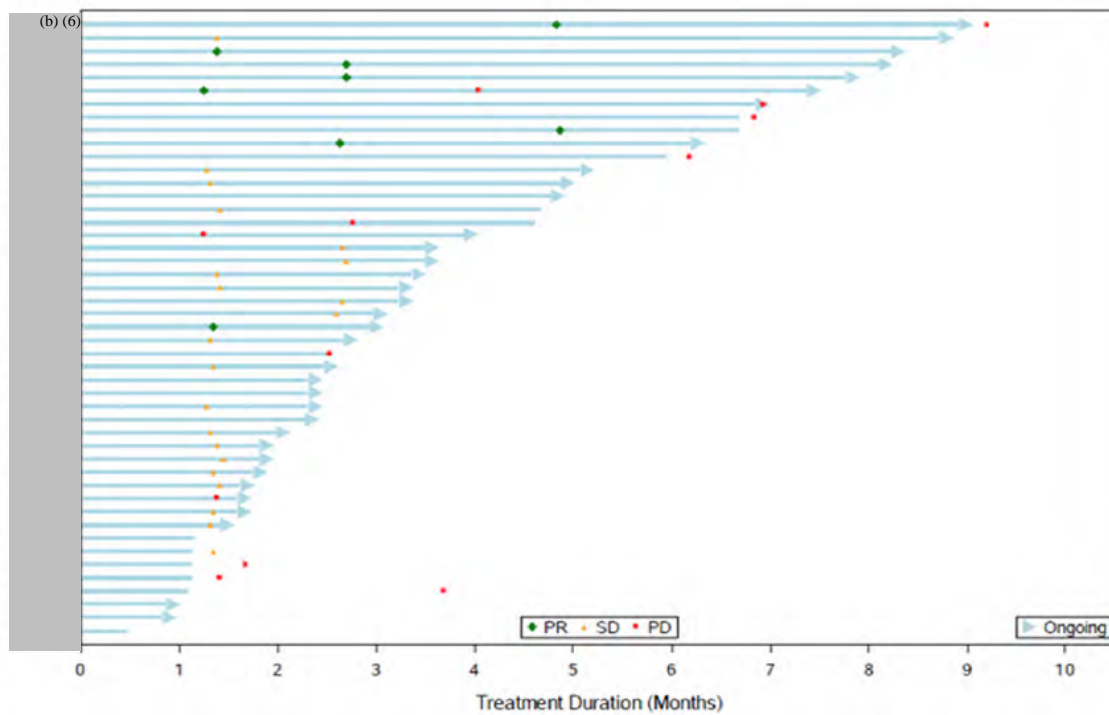
**Figure 1. INCB 54828-202: Waterfall plot of best percent change of target lesion size from baseline in Cohort A as assessed by IRC**



Source: Meeting package, page 28

Figure 2 provides a swimmer plot illustrating duration of treatment in Cohort A as assessed by IRC. The duration of response appears to range from approximately 1.5 months to 8.5 months with a median of approximately 5 months.

**Figure 2. Swimmer plot of treatment duration in Cohort A as assessed by IRC (confirmed)**



Source: Meeting package, p. 30

A safety analysis was performed on 87 patients. Treatment-emergent adverse events occurring in greater than 10% of patients included hyperphosphatemia (56%), diarrhea, nausea, vomiting, and stomatitis.

#### *INCB 64828-302*

Incyte proposes to conduct Study INCB 54828-302, an open-label, randomized, active-controlled, multicenter study of INCB054828 for the first-line treatment of patients with unresectable or metastatic cholangiocarcinoma with FGFR2 rearrangement. Eligible patients are those with previously untreated unresectable and/or metastatic cholangiocarcinoma with FGFR2 rearrangement based on local genomic testing (confirmatory testing will be performed on all patients). Patients with corneal or retinal disorders are ineligible for enrollment. Patients with a history of calcium and phosphate hemostasis disorders or those with ectopic calcification of soft tissues as well as gastrointestinal disorders that can raise gastric or small intestinal pH are also ineligible.

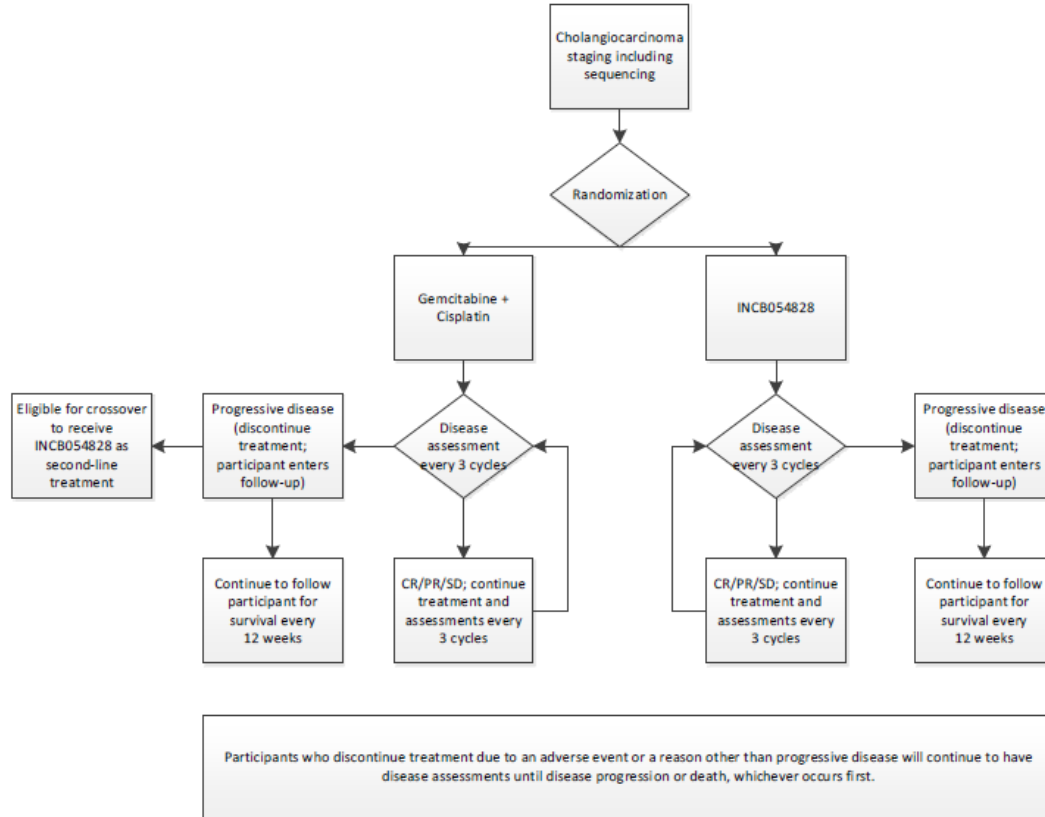
Randomization will be stratified by geographic region (West vs. Asia vs. rest of world) and by tumor stage (locally advanced vs. distant metastasis). Eligible patients will be randomly assigned in a 1:1 ratio to one of two treatment arms:

- Experimental: INCB054828 (13.5 mg orally daily) administered on a 2-week-on and 1-week-off schedule (one cycle is 3 weeks)
- Control: gemcitabine (1000 mg/m<sup>2</sup>) and cisplatin (25 mg/m<sup>2</sup>) administered by intravenous infusion on Days 1 and 8 every 3 weeks for up to 8 cycles

Treatment will continue until disease progression per RECIST v1.1 as assessed by an independent review committee (IRC), unacceptable toxicity, or withdrawal of consent. Patients who progress on gemcitabine plus cisplatin may be offered INCB054828 as second-line treatment at the time of investigator-assessed disease progression. See Figure 3 for the study schema.



**Figure 3. Study Schema**



Source: Taken from the meeting package, page 56

Tumor assessments will be conducted every 9 weeks.

The primary endpoint is progression free survival (PFS) as assessed by an independent review committee (IRC) per RECIST 1.1. Assuming that the median PFS is 8 months in the control arm and 11.4 months in the experimental arm, a total of 339 events are needed to detect a hazard ratio of 0.70 with 90% power at a 1-sided alpha level of 2.5%. The primary analysis will be a stratified log-rank test performed on the intent-to-treat (ITT) population.

One interim analysis will be performed after 119 (35%) PFS events for efficacy and futility. The Hwang-Shih-DeCani spending functions with parameters 4 and 2 for alpha- and beta-spending are used to determine boundaries for early termination of the study at the interim analysis.

Secondary efficacy endpoints include overall response rate (ORR) and overall survival (OS). If PFS is significant, then ORR will be tested at 0.025 (1-sided). No other efficacy endpoints will be included in the multiplicity adjustment.

## **SPONSOR QUESTIONS AND RESPONSES**

1. Does the Agency agree with the proposed patient population to be studied?

**FDA Response:** FDA does not object to treatment of patients with INCB054828 in the first-line setting provided that patients are adequately consented about the availability of therapy that has been shown to prolong survival. However, the primary analysis population should be limited to those identified using an analytically validated assay for FGFR2 rearrangements. Therefore, FDA strongly recommends that the trial not be initiated until the analytically validated assay to be marketed as a companion diagnostic test with INCB054828 is available for use at clinical sites for patient selection. See FDA additional comments.

2. Does the Agency agree with the primary endpoint of progression-free survival (PFS) defined as the time from date of randomization until date of disease progression according to RECIST v 1.1 and assessed by independent central reviewer (ICR) or death, whichever occurs first?

**FDA Response:** Because overall survival (OS) is a direct measure of clinical benefit and because radiographic findings on liver and biliary tract imaging may be difficult to interpret, OS is the preferred regulatory endpoint to support approval in patients with unresectable and/or metastatic cholangiocarcinoma. A robust improvement in PFS that is large in magnitude, statistically persuasive, and associated with an acceptable risk-benefit profile may support approval in the first-line setting; however, it is unlikely that the targeted magnitude of improvement in median PFS of 3.4 months will be of sufficient magnitude to verify and confirm the clinical benefit of INCB054828.

3. Does the Agency agree with the proposed dose of INCB054828 13.5 mg PO QD given in a 3-week cycle (2 weeks on therapy / 1 week off therapy)?

**FDA Response:** FDA has no objections to the dosage regimen of INCB054828 to be administered.

4. Does the Agency agree with comparator arm of gemcitabine/cisplatin?

**FDA Response:** FDA has no objections to the proposed comparator arm. In order for results to be relevant to the U.S. population, dose modification instructions in the protocol should be consistent with U.S. standard of care.

5. Does the Agency agree with the allowance of a crossover from the chemotherapy arm to INCB054828?

**FDA Response:** The proposal to offer INCB054828 to patients in the control arm at the time of investigator-assessed disease progression may confound any overall survival benefit. It is Incyte's risk to incorporate such a design into the protocol.

6. Does the Agency agree with the proposed statistical analyses?

**FDA Response:** FDA agrees with the proposed analysis methods for primary (PFS) and the secondary efficacy endpoints (ORR and OS). However, FDA has the following comments.

- a. FDA does not object to the interim analyses for futility purposes. However, FDA strongly recommends removing the plan of the study being stopped early for efficacy based on the interim analysis result of PFS because the estimation of treatment effect may not be robust and reliable based on 35% of information. In addition, Incyte should consider the adequacy of data with regard to other issues such as safety, duration of benefit, outcomes in important subgroups and important secondary endpoints.
- b. FDA recommends using O'Brien-Fleming spending function to determine alpha allocation for the interim analysis and final analysis based on the actual information fraction. FDA suggests that a very small alpha be allocated to the interim analysis (for futility purpose) because efficacy data will be analyzed in the analysis. Please specify the futility stopping boundary as non-binding.
- c. Whether the proposed primary analysis population of all randomized patients is acceptable will depend upon the assay method used for selection of patients for enrollment of the trial. Please see FDA's response to Question 1.
- d. Please be advised that two Phase 3 studies are generally required for a marketing approval. FDA would accept a single pivotal study to support a marketing approval if results show a highly statistically significant and clinically meaningful treatment effect on a measure of clinical benefit that is internally consistent across relevant subgroups. The results of the single pivotal trial should be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products" at <http://www.fda.gov/cder/guidance/index.htm>.

7. Does FDA agree that an application for Breakthrough Therapy Designation is appropriate given the preliminary clinical results of study INCB 54828-202?

**FDA Response:** FDA does not agree that the available clinical results of Study INCB 54828-202 will satisfy the Breakthrough Therapy Designation (BTD) criterion for preliminary clinical evidence that the drug may demonstrate substantial improvement over available therapies. In order to support BTD based upon overall response rate (ORR) data derived from a single arm trial, the magnitude of ORR and durability of responses should be large enough to be clinically meaningful and also represent an improvement over available therapy. All responders should be followed for a minimum of 6 months from the onset of response to adequately characterize durability of

response. Given the relatively modest ORR observed and lack of historical information regarding the ORR conferred by standard treatments for cholangiocarcinoma harboring FGFR2 translocations in the second or later-line settings, response durability will be a key factor in a BTD determination. FDA recommends that Incyte seek a preliminary BTD advice teleconference to discuss a potential BTD application when sufficient follow-up data are available. With this request, provide a subject-level listing that includes duration of treatment, best overall response, time from initiation of treatment to onset of response, and duration of confirmed response. Note that FDA considers the denominator for ORR to be the number of patients with FGFR2 translocations treated with INCB054828, not the number of “evaluable” patients.

## **Additional Comments**

### **Clinical**

8. FDA considers the evaluable population in Study INCB054828-202 to be the “as-treated” population defined as all patients who received one or more doses of INCB054828 and in Study INCB054828-302 to be the intent-to-treat population (all randomized) population. Therefore, FDA has revised Incyte’s response data for Protocol INCB 54828-202 to include those patients without follow up imaging as part of the denominator (i.e., 47 patients and not 45).
9. FDA recommends that Incyte consider using the same diagnostic assay for FGFR2 rearrangements (i.e., FMI FGFR Clinical Trial Assay from Foundation Medicine, Inc.) for Protocol INCB 64828-302 that is currently being used in Protocol INCB 54828-202. See CDRH additional comments below.
10. Because the patient population for Protocol INCB 64828-302 will not have received prior therapy, FDA encourages Incyte to consider the use of an add-on design (e.g., chemotherapy with INCB054828 vs. chemotherapy with placebo).

### **Clinical pharmacology**

Revise Protocol INCB 54828-302 to address the following:

11. Exclude patients with renal impairment (serum creatinine clearance <60 ml/min) as cisplatin is contraindicated in patients with preexisting renal impairment.
12. Include additional ECG monitoring around the C<sub>max</sub> for INCB054828 after first dose and after repeat doses. Submit QT assessment plan with available data for the FDA QTIRT review. Once the QT risk has been ruled out, a reduced monitoring plan may then be initiated.
13. Include a sparse pharmacokinetic sampling plan beyond cycle 1 for population PK and exposure-response analyses.

14. Restrict the use of medications with a narrow therapeutic index that known to be metabolized by CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4/5 as the potential of INCB054828 to induce these metabolic enzymes has not been assessed.

During the development of INCB054828 evaluate the potential of INCB054828 to induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5. Refer to FDA guidance for Industry, entitled “In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies Guidance for Industry” available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>

### **Center for Devices and Radiological Health (CDRH)**

15. Incyte stated that “participant eligibility can be based on local genomic testing results, if available, and that confirmatory testing through the sponsor's central genomics laboratory must be performed on all participants”. However, in question 1, Incyte also said that “Subjects must have documented FGFR2 rearrangement reported by the Sponsor central laboratory or have documented FGFR2 rearrangement reported by a certified local or central laboratory.” Clarify whether a single central test or multiple local tests will be used for patient enrollment, and specify the proposed central lab test that will be used for confirmation and if those patients who are positive for FGFR2 rearrangement by a local test, but cannot be confirmed by the central testing will be enrolled in the trial.
16. If Incyte uses test results obtained from a variety of laboratory-developed tests (LDT), the concordance between testing methods (e.g., fusions assessed and analytical sensitivity) is not known. A preferred approach is either (1) to employ one test/method, using the same analytically validated reagents and procedure for testing and result reporting, at all testing sites, or (2) to have all patients screened by a single, analytically validated test at a central laboratory. The testing plan, to the extent that it is currently understood, poses (1) risk of diluting the apparent effectiveness of the drug if some of the local tests perform poorly, and/or (2) risk of ambiguity in defining the intent-to-treat population, with uncertainty for generalizing the trial results to post-approval use of the drug where the indication will specify identification of patients through use of a FDA approved test.
17. Indicate the pre-specified fusions and cut-off(s) for each assay that will be used to determine patient selection for enrollment into the trial.
18. Since a diagnostic test will be essential for the safe and effective use of this therapy, then a companion diagnostic test would be required for approval of the drug, and a regulatory submission (PMA) would be needed to establish the performance of the test with the drug. The following FDA Guidance for Industry and Food and Drug Administration Staff documents may be helpful:

“In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff” available at

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>

“Requests for Feedback on Medical Device Submissions: Guidance for Industry and Food and Drug Administration Staff” available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>

## **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Since INCB054828 has orphan designation for the treatment of cholangiocarcinoma and therefore, is exempt from PREA requirements for the cholangiocarcinoma indication at this time; however, if there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change. Additionally, Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that original marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

For additional guidance on the timing, content, and submission of an initial Pediatric Study Plan (iPSP), including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov). For further guidance on pediatric product development, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

## **DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.



For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

## **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

## **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

## **SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

## **OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions



(February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

### **NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
  - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
  - Other significant changes
  - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STACIE A WOODS  
05/08/2018