CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214622Orig1s000

OTHER REVIEW(S)

Consult Memorandum

Date:	May 19, 2021
To:	Christina Leach (RPM) and Loraine Pelosof/Sandra Casak, MOs, CDER/OHOP/DOP1
From:	Deb K. Chatterjee, CDRH/OIR/DMGP/MPCB
ICCR Number:	00034897
Subject:	NDA 214622
Drug Name:	Infigratinib
Drug Sponsor	QED Therapeutics
Biomarker(s):	*FGFR2 Fusion/Rearrangements*
Device Name:	F1 CDx
Device Sponsor:	Foundation Medicine
Related Submissions:	P170019/S021

I. BACKGROUND and PURPOSE

The purpose of this NDA submission was to get approval of the drug infigratinib for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations detected by FoundationOne CDx (F1CDx) device. The results will be based on results from Study CBGJ398X2204.

II. DRUG DESCRIPTION and PROPOSED INDICATION

Drug: Infigratinib.

Indication: Treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements, as detected by an FDA approved test.

III. PROPOSED DEVICE IN THE TRIAL

Foundation One CDx (F1CDx)

IV. TRIAL OVERVIEW AND REVIEW SUMMARY

Study Title: A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with *FGFR2* gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy

Study Design

There were 3 cohorts in the study:

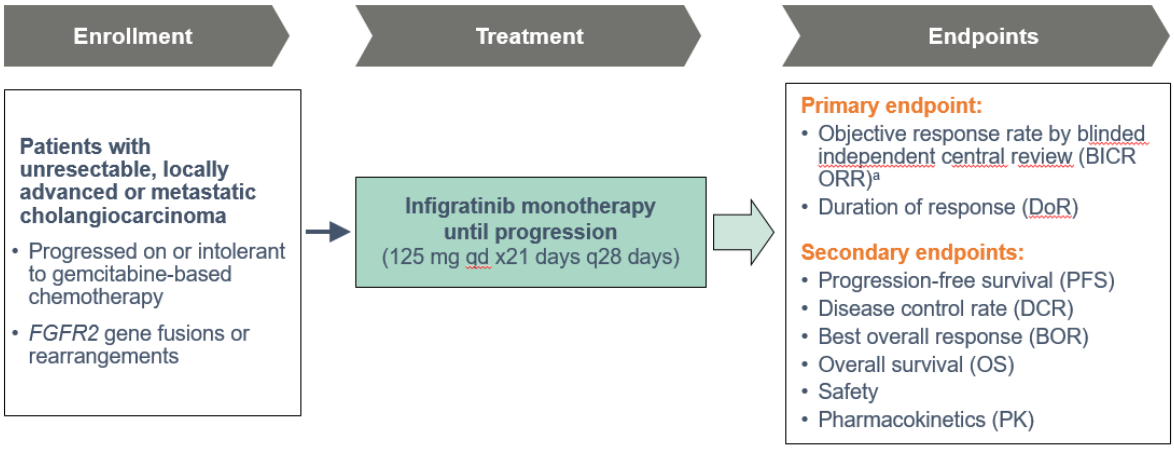
Cohort 1: Patients with FGFR2 gene fusions/rearrangements and FGFR2 negative patients (NDA population in the clinical trial—will be used for bridging study).

Cohort 2: Patients with advanced or metastatic cholangiocarcinoma with specific FGFR genetic alterations other than FGFR2 rearrangement

Cohort 3: Patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations who have received a prior FGFR inhibitor excluding BGJ398 (infigratinib).

Results for Cohorts 2 and 3 are not provided in this interim report (Exploratory).
The summary of study design for cohort 1 is shown in Fig. 1 below:

Figure1: Cohort 1 of Phase 2 single-arm study CBGJ398X2204



Key Inclusion criteria:

- Patients (≥ 18 years of age) with histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis.
- Patients with cancers of the gallbladder or ampulla of Vater are not eligible.
- Written documentation of local laboratory or central laboratory determination of the FGFR2 gene alterations from a sample collected before BGJ398 treatment.
- An archival tissue sample must be available with sufficient tumor for central FGFR gene alteration molecular testing.
- Evidence of measurable disease according to RECIST Version 1.1.

Key Exclusion criteria:

- Prior or current treatment with a mitogen-activated protein kinase (MEK) inhibitor, BGJ398/infigratinib (or selective FGFR inhibitor).
- Neurological symptoms related to underlying disease requiring increasing doses of corticosteroids.

REVIEW:

The applicant (QED Therapeutics) partnered with Foundation Medicine to submit a supplemental PMA for the qualitative detection of *FGFR2* fusion/rearrangements from nucleic acids isolated from formalin-fixed, paraffin-embedded cholangiocarcinoma tissue using FoundationOne CDx (F1 CDx). Samples were originally screened using local and central tests for the clinical trial treatment with infigratinib. 108 samples with confirmed *FGFR2* fusion/rearrangements by clinical trial assays (CTAs) were enrolled in CBGJ398X2204 registrational study. Of the 108 patients that had a biomarker-positive *FGFR2* fusion/rearrangement by CTAs, 69 had FFPE tissue or sufficient remaining DNA mass from the CTA or central confirmatory F1 testing to be retested by F1CDx; these samples were assessed in the F1CDx-evaluable set. Thirty-nine (39) patient samples had insufficient DNA mass (<50 ng) and were included in the F1CDx non-evaluable set. Sensitivity analysis was used to estimate the efficacy for these 39 samples.

The positive percent agreement (PPA) and negative percent agreement (NPA) concordance study between the F1CDx assay and the CTA assays demonstrated 96.67% and 100.00% agreement, respectively. The clinical bridging study estimated an overall response rate (ORR) of 28.07% for the F1CDx *FGFR2* fusion/rearrangement positive population, which demonstrated the clinical efficacy of using F1CDx as the CDx assay compared to the ORR of 23.15% for the CTA *FGFR2*-positive population (NDA). The sensitivity analysis of clinical efficacy for the F1CDx positive population ranged from 21.68% to 22.49% per the average among the imputed data sets.

The data support the reasonable assurance of safety and effectiveness of the device when used in accordance with the indications for use. The use of this device to aid clinicians in identifying cholangiocarcinoma patients who may be eligible for treatment with infigratinib based on FGFR2 fusion/rearrangement detected result is expected to provide a benefit in overall response rate.

In summary, considering all factors including conditions of approval (post-market actions), the benefits of the use of F1CDx in patients with cholangiocarcinoma as an aid for selecting patents for treatment with infigratinib are judged to outweigh the risks.

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.

/s/

CHRISTINA L LEACH
05/20/2021 12:11:29 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 17, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 214622
Product Name and Strength:	Truseltiq (infigratinib) Capsules, 25 mg and 100 mg
Applicant/Sponsor Name:	QED Therapeutics
OSE RCM #:	2020-1809-2
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 7, 2021 for Truseltiq. Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Truseltiq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Stewart J. Label and Labeling Review Memorandum for Truseltiq (NDA 214622). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 30. RCM No.: 2020-1809-1.

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

---

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

/s/

JANINE A STEWART
05/17/2021 05:42:54 PM

ASHLEIGH V LOWERY
05/18/2021 04:56:04 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 30, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 214622
Product Name and Strength:	Truseltiq (infigratinib) Capsules, 25 mg and 100 mg
Applicant/Sponsor Name:	QED Therapeutics
OSE RCM #:	2020-1809-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 9, 2021 for Truseltiq. Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Truseltiq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We provide specific recommendations to QED Therapeutics in Section 3 below.

[a] Stewart J. Label and Labeling Review for Truseltiq (NDA 214622). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-1809.

3 RECOMMENDATIONS FOR QED THERAPEUTICS

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

A. Container Labels

1. Revise the header that reads “Treatment-Free Days” to read “Days 22-28 - Treatment Free Days “ for continuity of the column headers and to improve clarity.
2. Revise the strength statements on the bister cards that read “25 mg or 100 mg” to read “25 mg per capsule” and “100 mg per capsule”. We recommend this to clarify that the stated strength is per capsule.

B. Carton Labeling

1. For the cartons of the 50 mg and 100 mg strengths and the inner cartons of the 75 mg strength, remove (b) (4) . This is recommended to reduce (b) (4) .

C. Carton Labeling (75 mg daily dose; outermost carton which contains 2 blister cards)

1. To reduce redundancy and to improve clarity, revise the net quantity statement to read:

Contains two blister cards for one treatment cycle (63 capsules total)

Days 1-14	Days 15-28
25 mg	25 mg
42 capsules	21 capsules

D. Carton Labeling (75 mg daily inner cartons)

1. To reduce redundancy and to improve clarity, revise the net quantity statement on the carton containing Days 1-14 to read:

Blister card contains

Days 1-14
25 mg
42 capsules

a. To prompt users to continue with treatment cycle days 15-28, add a statement to the end of the dosing instructions for days 1-14 such as “To complete this 28-day cycle, continue with the Days 15-28 blister card”.

2. To reduce redundancy and to improve clarity, revise the net quantity statement on the carton containing Days 15-28 to read:

Blister card contains

Days 15-21	Days 22-28
25 mg	
21 capsules	Treatment-free days.

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

---

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

/s/

JANINE A STEWART
05/03/2021 02:16:16 PM

ASHLEIGH V LOWERY
05/03/2021 02:17:10 PM

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

PATIENT LABELING REVIEW

Date:	March 24, 2021
To:	Christina Leach Regulatory Project Manager **Division of Oncology 3 (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRUSELTIQ (infigratinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 214622
Applicant:	QED Therapeutics, Inc.

1 INTRODUCTION

On September 29, 2020, QED Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214622 for TRUSELTIQ (infigratinib) capsules. The proposed indication for TRUSELTIQ (infigratinib) capsules is for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test. We note that the proposed proprietary name TRUSELTIQ was found to be conditionally acceptable on December 28, 2020 by the Division of Medication Error, Prevention, and Analysis (DMEPA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 3 (DO3) on October 2, 2020 and October 27, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRUSELTIQ (infigratinib) capsules.

2 MATERIAL REVIEWED

- Draft TRUSELTIQ (infigratinib) PPI received on September 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 11, 2021.
- Draft TRUSELTIQ (infigratinib) Prescribing Information (PI) received on September 29, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 11, 2021.
- Approved PEMAZYRE (pemigatinib) tablets comparator labeling dated February 23, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

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

/s/

JESSICA M CHUNG
03/24/2021 09:36:43 AM

EMILY M DVORSKY
03/24/2021 09:56:51 AM

SHARON R MILLS
03/24/2021 10:00:17 AM

LASHAWN M GRIFFITHS
03/24/2021 10:08:49 AM

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

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

Memorandum

Date: March 22, 2021

To: Christina Leach, PharmD, Regulatory Project Manager
Division of Oncology 3 (DO3)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for [TRADENAME] (infigratinib) capsules, for oral use

NDA: 214622

In response to DO3 consult request dated October 27, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for [TRADENAME] (infigratinib) capsules, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Christina Leach) on March 10, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DO3 (Christina Leach) on March 16, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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

---

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

/s/

EMILY M DVORSKY
03/22/2021 09:35:12 AM

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

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

Date of This Review:	March 22, 2021
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 214622
Product Name, Dosage Form, and Strength:	Truseltiq (infigratinib) Capsules, 25 mg and 100 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	QED Therapeutics
FDA Received Date:	September 29, 2020, November 5, 2020, November 23, 2020, December 22, 2020, February 4, 2021
OSE RCM #:	2020-1809
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Truseltiq (infigratinib) Capsules, the Division of Oncology 3 (DO3) requested that we review the proposed Truseltiq prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B– N/A
Human Factors Study	C– N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Request	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, container labels, and carton labeling for Truseltiq (infigratinib) to identify deficiencies that may lead to medication errors and other areas of improvement. To inform our review, we issued an Information Request to the Applicant on March 1, 2021 to clarify if the Applicant collected any usability data for use of the proposed packaging configuration and labeling in the intended user population (see Appendix F). In their March 5, 2021 response (See Appendix F), the Applicant stated that they had not collected any usability data for their proposed product, but cited general data supporting the usability of calendar blister pack configurations from published literature and data provided by the manufacturer of the proposed packaging. Our review identified areas of the PI, container labels and carton labeling that can be modified to improve the clarity of the information presented.

The dosing interval of the proposed product is 21 consecutive days of treatment followed by 7 days off treatment for each 28-day cycle. As proposed the container labels and carton labeling use varying language to describe the treatment interval (e.g. (b) (4) 'Days 1-21'). Also, the dosing instructions and the net quantity statements on the proposed carton labeling can be optimized for clarity. Further, we note that the different strength configurations can be

better differentiated by color to prevent selection errors. We note that Section 16 How Supplied/Storage and Handling can be revised for clarity and for consistency with the container labels and carton labeling.

4 CONCLUSION & RECOMMENDATIONS

Our review of materials found that the proposed Truseltiq PI, container labels, and carton labeling may be improved to promote safe and effective use of this product. Thus, we provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. How Supplied/Storage and Handling Section
    a. Consider revising the presentation of information in Section 16: How Supplied/Storage and Handling for clarity and consistency with the container labels and carton labeling; for example, as follows:

TRUSELTIQ (infigratinib) capsules are available in the strengths and packages listed below:

- 25 mg: Hard gelatin capsule (b) (4) a white opaque body (b) (4) gray opaque cap - imprinted with black text on the body – INFI 25mg
- 100 mg: Hard gelatin capsule (b) (4) a white opaque body (b) (4) light orange opaque cap - imprinted with black text on the body – INFI 100mg

TRUSELTIQ capsules are supplied in 21-day blister pack dose presentations as follows:

- 50 mg daily dose: Each carton contains 1 blister card containing a 21-day supply (42 capsules; 25 mg infigratinib per capsule). [NDC-72730-506-01].
- 75 mg daily dose: Each carton contains 2 blister cards containing a 21-day supply (63 capsules; 25 mg infigratinib per capsule). [NDC-72730-202-01].
- 100 mg daily dose: Each carton contains 1 blister card containing a 21-day supply (42 capsules; 100 mg infigratinib per capsule). [NDC-72730-111-01].
- 125 mg daily dose: Each carton contains 1 blister card containing a 21-day supply ((b) (4) (b) (4) 21 capsules, 100 mg infigratinib per capsule and 21 capsules; 25 mg infigratinib per capsule). [NDC-72730-101-01].

4.2 RECOMMENDATIONS FOR QED THERAPEUTICS

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

A. General Comments (Container labels & Carton Labeling)

1. We note the currently proposed [redacted] color scheme for the proposed 125 mg carton and container overlaps in color with both the proposed 100 mg [redacted] and the 75 mg [redacted] configurations. The use of similar and overlapping colors utilized in highlighting the strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. We recommend revising the color scheme of the 125 mg packaging configuration to a non-similar color to the other configurations in the product line.

B. Container Labels

1. [redacted] Revise the headers for each column of the blister card to read "Days 1-7, Days 8-16, etc. …" .
    a. As currently proposed the sub header for the [redacted] Day 22-28 column reads [redacted]. Revise the sub header to read "Treatment-free days".
2. We are concerned that users will have difficulty keeping track of their daily dose schedule and treatment-free period. Revise the "Start date:___" blank to read "Enter start date:___" to prompt the user to use this date as a marker to optimize compliance with the treatment schedule.

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the "[redacted]" statement on the back panel to read "Recommended Dosage: See prescribing information."
    a. Relocate this statement to appear underneath the strength statement.
2. Revise the strength and dosage statements to support patient comprehension regarding the capsule combinations required to achieve the stated dosage
    a. Example (not true to layout, size, spacing, color, etc.):

125 mg daily dose
Take one 100 mg capsule and one 25 mg capsule once daily.

3. [redacted] Revise the net quantity statement to express the carton contents in terms of day supply; [redacted]. Additionally, revise to include the total quantity of capsules contained in the carton. For example:

> Blister pack contains one treatment cycle (42 capsules total)
>
> Days 1-21:
>
> | | |
> |---|---|
> | 100 mg | 25 mg |
> | 21 capsules | 21 capsules |
>
> Days 22-28: Treatment-free days.

4. As proposed, the Dosing Instructions on the back panel are incomplete and appear in small font.
   a. To create space to clarify the dosing instructions and to increase the font size for improved readability, consider relocating the distributor logo and contact information to appear within the graphic in the right column of the back panel.
   b. Omit the "[redacted]" statement to eliminate redundancy.
   c. Revise the dosing information according to the following example:

> Dosing Instructions:
> Take Truseltiq for 21 consecutive days. Then take a 7 day break [redacted] 28-day treatment cycle before staring the next 28-day treatment cycle.
>
> Days 1-21: Take x capsules once daily on an empty stomach (1 hour before or 2 hours after a meal). Swallow capsules whole with a [redacted] glass of water. Do not open, crush, chew, or dissolve capsules.
>
> Days 22-28: Treatment-free days. Do not take any doses for 7 days.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Truseltiq received on December 22, 2020 from QED Therapeutics.

Table 2. Relevant Product Information for Truseltiq	
Initial Approval Date	N/A
Active Ingredient	infigratinib
Indication	Treatment of adults with previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma with FGFR2 fusion or other rearrangements
Route of Administration	Oral
Dosage Form	Capsules
Strength	25 mg and 100 mg
Dose and Frequency	Usual dose: 125 mg (administered as one 100 mg capsule plus one 25 mg capsule) orally once daily on days 1-21 of each 28-day cycle, at least 1 hour before or 2 hours after a meal. • 1st dose reduction: 100 mg (one 100 mg capsule) • 2nd dose reduction: 75 mg (three 25 mg capsules) • 3rd dose reduction: 50 mg (two 25 mg capsules)
How Supplied	• Blister pack for 50 mg daily dose (Contains 21 doses of two 25 mg capsules: Dosage equal to 50 mg per day) • Blister packs for 75 mg daily dose (Contains 21 doses of three 25 mg capsules. Dosage equal to 75 mg per day) • Blister pack for 100 mg daily dose (Contains 21 doses of 100 mg capsules) • Blister pack for 125 mg daily dose (Contains 21 doses of 100 mg and 25 mg capsules. Dosage equal to 125 mg per day)
Storage	20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F)
Container Closure	packaged in (b) (4) blister pocket material with foil lidding contained in cardboard based packs.

APPENDIX F. INFORMATION REQUEST

F.1 Information Request (IR)

On March 1, 2021 we sent a request via email for information to inform our review of the proposed packaging configuration and labeling. We asked QED to clarify if they collected any usability data for use of the proposed packaging configuration and labeling in the intended user population.

F.2 Response

The Applicant responded to our IR on March 5, 2021. In their response, QED stated that they had not collected any usability data for their proposed product, but cited general data supporting the usability of calendar blister pack configurations from published literature and data provided by the manufacturer of the proposed packaging.

Report available in docuBridge via:

\\CDSESUB1\evsprod\nda214622\0023\m1\us\111-info-amend\quality-infor-amendment-dmepa.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container label received on February 4, 2021
- Carton labeling received on February 4, 2021
- Prescribing Information (Image not shown) received on December 22, 2020, available from \\CDSESUB1\evsprod\nda214622\0012\m1\us\114-labeling\114a-draft-label\draft-uspi-clean.docx

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

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

---

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

/s/

JANINE A STEWART
03/22/2021 01:59:12 PM

ASHLEIGH V LOWERY
03/22/2021 02:42:07 PM

Clinical Inspection Summary

Date	03/5/2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Lorraine Pelosof, MD Sandra Casek, MD Lola Fashoyin-Aje, MD Christina Leach, PharmD. Regulatory Project Manager Division of Oncology (DO3) Office of Oncologic Diseases (OOD)
BLA #	214622
Applicant	QED Therapeutics, Inc.
Drug	Infigratinib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine kinase inhibitor
Proposed Indication	The treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA approved test
Consultation Request Date	October 22, 2020
Summary Goal Date	March 14, 2021
Action Goal Date	May 14, 2021
PDUFA Date	May 29, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study CBGJ398X2204 were submitted to the Agency in support of a New Drug Application (NDA 214622) for infigratinib for the above proposed indication. Two clinical investigators (Drs. Roychowdhury and Javle) and the study sponsor (QED Therapeutics, Inc.) were selected for clinical inspections.

The protocol-required ophthalmic safety assessments performed at Dr. Roychowdhury's site lacked adequate documentation (including subject ID, date, name of person performing assessment) to ensure the reliability of the reported data. No additional significant data concerns were identified at either clinical investigator site or at the QED Therapeutics. Specifically, there were no significant unreported adverse events or protocol deviations, and the secondary endpoint data regarding overall survival were verified.

Although regulatory violations were identified at all three inspected entities which are discussed under the results section of this document, none of the violations had a significant impact on subject safety or data integrity. The study thus appears to have been conducted adequately and except for the lack of adequate documentation for ophthalmic safety assessments at Dr. Roychowdhury's site, the data generated by the inspected clinical investigators and the sponsor appear to be acceptable in support of the NDA.

II. BACKGROUND

QED Therapeutics, Inc. seeks approval of infigratinib for the treatment of patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma. In support of the NDA, the Applicant submitted clinical data from Study **CBGJ398X2204** (NCT02150967), titled "A phase II multicenter, single arm study of oral BGJ398 in adult patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy."

Study CBGJ398X2204 is an open-label, single-arm trial of infigratinib in adult patients with advanced or metastatic cholangiocarcinoma.

Major inclusion criteria include adult subjects with

- histologically or cytologically confirmed cholangiocarcinoma;
- FGFR gene alteration confirmed by central or local laboratory determination;
- evidence of measurable disease according to RECIST version 1.1.

Subjects were prescreened for FGFR genetic alterations, then underwent additional screening for eligibility criteria within 21 days of dosing the study drug. Subjects were enrolled into 3 cohorts based on FGFR status. Cohort 1 initially consisted of subjects with FGFR2 genetic alterations. After January 24, 2017 when Protocol Amendment 2 went into effect, only subjects with FGFR2 gene fusions and translocations were enrolled into Cohort 1.

Starting with Protocol Amendment 4 (April 21, 2019), two additional cohorts were added: **Cohort 2**: Subjects with FGFR genetic alterations other than FGFR2 gene fusions or translocations; and **Cohort 3**: Subjects with FGFR2 gene fusions or translocations who have received a prior FGFR inhibitor excluding infigratinib. The Cohort of interest for this application is **Cohort 1**, subjects with FGRF2 gene fusions or translocations.

All subjects received infigratinib 125 mg by mouth once daily for 21 days (3 weeks) followed by 7 days (one week) off treatment, in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or death.

The **primary objective** was to evaluate the efficacy of single agent infigratinib in patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations or other FGFR genetic mutations. The **primary endpoint** was overall response rate (ORR), defined as the proportion of patients with a best overall response of Complete Response (CR)

or Partial Response (PR), assessed by central imaging review as per RECIST v1.1. A key **secondary endpoint** of interest was overall survival.

Subjects were assessed at baseline, within 28 days of the first dose, and were evaluated for tumor response according to RECIST 1.1 by CT or MRI every 8 weeks (on day 1 of every odd cycle). Safety assessments such as physical exam, vital signs, and labs including phosphate and calcium (because of concern for hyper- and hypophosphatemia and hypercalcemia) were performed at screening, day 1, 8, and 15 of cycle 1, days 1 and 15 of cycles 2 and 3, and day 1 of subsequent cycles. Ophthalmic assessments were performed at screening and day 15 of cycle 1, day 1 of cycles 2 and 3, and for subsequent cycles (i.e., after C3D1) were performed every 4 months (i.e., C7D1, 1 C11D problems1, C15D1, C19D1, etc.) because of concern for ocular disorders, including retinal or cornea disorders. Adverse events were assessed continuously.

Once the study drug was discontinued, subjects completed an End of Treatment (EOT) Visit within 14 days of the decision to discontinue treatment, followed by 30-day Safety Follow-up Visit. Thereafter, all subjects were followed for survival at least every 4 months after discontinuation of study drug. Subjects who discontinued the study drug for any reason other than disease progression had tumor assessments every 8 weeks until disease progression or the initiation of subsequent antineoplastic therapies, or death, whichever occurs first.

The first subject was treated on July 23, 2014 and the data cutoff for this application was March 31, 2020. A total 108 subjects with FGFR2 fusions in Cohort 1 had received at least one dose of the study drug.

III. RESULTS

1. **Dr. Sameek Roychowdhury (CI Site 5001)**
   Ohio State Comprehensive Cancer Center, James Cancer Hospital
   241 W 11th Ave., Ste 4055
   Columbus, OH, 43201, US
   Inspection dates: January 11 – 22, 2021

   This investigator was inspected as an on-site surveillance inspection for Study CBGJ398X2204. This was the first FDA inspection for this investigator.

   According to the enrollment logs at the site, 39 subjects were screened and 21 subjects were enrolled prior to the data cutoff date. Of the 21 enrolled subjects at the site, 15 had died, 5 were off treatment and on follow-up (3 had come off treatment for progressive disease and 2 for adverse events), and one subject continued on treatment. There were no discrepancies between the data listings and the site source records for enrollment and disposition. After the data cut-off date, site records indicate that one additional subject was enrolled at the site and remains on treatment (Subject 5001-(b) (6)), and one previously enrolled subject (Subject 5001-(b) (6)) had died.

The inspection reviewed the source data for 15 of 21 enrolled subjects and compared them to the data listings. The reviewed subject records included informed consents, eligibility criteria, subject medical records and electronic records including subject medical history, concomitant medications, vitals and physical exams, applicable labs, imaging and pathology, progress notes, adverse events, hospital records, and protocol deviations. The inspection also reviewed study records including Form FDA 1572s, financial disclosures, protocol and amendments, delegation of authority logs, monitoring logs, staff training records, IRB communications, Sponsor-site communications, IP investigational product (IP) administration records storage and accountability records, electronic case report forms, EDC functionality and audit records.

The primary endpoint was based on independent central review of imaging. All imaging studies performed at the site for study scheduled assessments were correctly submitted to the central radiology facility. The site records indicated that there were several imaging studies performed on study subjects outside of the protocol-scheduled imaging timepoints for which there was no imaging result in the data listings. According to the imaging charter, scans performed outside of the scheduled time points were to be read in the same manner as scans performed for scheduled assessments. For three study subjects (see Table 1), the missing imaging data was from CT/MRI examinations performed after the end of treatment, while the subjects were in the follow-up phase of the study. The site had not sent the imaging studies to the central radiology facility.

Table 1: Imaging studies missing from the data listings, performed after the end of study drug treatment, during follow-up

Subject ID	1st IP dose	End of treatment date, reason	Last imaging date and result from data listings	Missing imaging date and study
5001- (b) (6)	(b) (6)	(b) (6), PD	(b) (6), PD	6/23/2018 CT Abd/Pel for flank pain
5001- (b) (6)	(b) (6)	(b) (6), AE	(b) (6), PR	2/6/2020 CT Chest/Abd/Pel for staging
5001- (b) (6)	(b) (6)	(b) (6), PD	(b) (6), SD	3/17/2020 CT Abd/Pel for abdominal pain, elevated bilirubin
				3/18/2020 MRCP, for elevated bilirubin

Reviewer's Comments: In the cases of Subject 5001-(b) (6) and Subject 5001-(b) (6), disease progression had been established prior to the date of the missing CT and thus would not have impacted any study endpoints. In the case of Subject 5001-(b) (6), the previous imaging data point demonstrated partial response. However, the missing imaging data would not have affected any study endpoints for the current analysis because the subject was censored prior to the date of the missing imaging study. There was no evidence of harm to subjects as all of the studies were interpreted locally and the results were communicated to the clinical investigator.

For two of the study subjects, CT imaging data was missing from dates prior to the end of treatment with the study drug, as shown in Table 2. Subject 5001-(b) (6) had a CT of the abdomen and pelvis on (b) (6) for right upper quadrant pain, in between scheduled follow-up time points 2 and 3. The site did not send the CT to the central radiology facility. Subject 5001-(b) (6) had three CT exams, all within a month of starting treatment. The subject was taken off study for clinical disease progression before undergoing the first scheduled CT assessment. The site sent the CTs dated (b) (6) and (b) (6) to the central imaging facility, but no records of the studies is included in the efficacy data listings.

Table 2: Imaging assessments missing from data listings (shaded rows)

Subject	First IP dose	End of treatment date, reason	Imaging dates, study indication	BICR Result	Local Radiology Result
5001-(b) (6)	(b) (6)	(b) (6), PD	(b) (6) – per protocol	SD	SD
			(b) (6) – per protocol	SD	PD
			(b) (6) – CT abd/pel for RUQ pain	---	Widespread lung, liver, and bone metastases
			(b) (6) – per protocol	SD	PD
			(b) (6) – per protocol	PD	PD
5001-(b) (6)	(b) (6)	(b) (6), clinical PD	(b) (6) - CT chest for restaging	---	Pulmonary metastases and lymphadenopathy
			(b) (6) – CT abd for elevated bilirubin	---	Liver metastases and lymphadenopathy
			(b) (6) – MRI abd for elevated bilirubin	---	Liver metastases and lymphadenopathy

Reviewer's Comments: Subject 5001-(b) (6) did not achieve response during the study, and thus the missing data could not have affected the primary endpoint. It is possible that the missing scan could have negatively impacted the secondary endpoint PFS if the missing CT had been interpreted as disease progression by BICR.

Subject 5001-(b) (6) also never achieved a response so the missing imaging studies could not have affected the primary endpoint, however, they could have affected the secondary endpoint of PFS. The PFS is reported as 1.77 months in the data listings and would have been <0.5 months if the missing CT was read as disease progression. There was no evidence of harm to subjects as all of the studies were interpreted locally and the results were communicated to the clinical investigator.

There were unreported protocol deviations at the site, namely, three of the enrolled subjects at the site had failed to meet the eligibility criteria. Subjects 5001-(b) (6) and 5001-(b) (6) (both enrolled in January of (b) (6)) did not meet the eligibility requirement for FGFR2 gene fusions or translocations as per Protocol Amendment 2/Version 2 (1/24/2017) in effect at the time. Subject 5001-(b) (6) had an ECOG performance status of 2 at screening, and thus did not meet the eligibility criteria for ECOG performance status of ≤ 1.

Reviewer's Comments: The enrollment of Subjects 5001-(b) (6) and 5001-(b) (6) is preapproved in an email correspondence between Novartis (the sponsor at the time) and Dr. Roychowdhury. These subjects are excluded from the analysis population for this submission. Subsequent protocol versions allowed for the enrollment of subjects with other FGFR2 genetic alterations.

The enrollment of Subject 5001-(b) (6) with an ECOG of 2 on (b) (6) is not described as a protocol deviation in the submitted data listings. Dr. Rowchowdhury requested approval to enroll from the sponsor on 3/16/2019, over one month after the subject received the first dose of the study drug ((b) (6)). According to source records at the site, the subject subsequently was reported as having an ECOG performance status of 1 and there was no evidence of harm to the subject related to enrollment in the study.

Three serious adverse events were not reported to the sponsor within the protocol required 24-hour time frame, specifically: Subject 5001-(b) (6) was hospitalized for vascular insufficiency, Subject 5001-(b) (6) was hospitalized for vomiting, and Subject 5001-(b) (6) had spontaneous nocturnal erections. Additionally, the SAE for Subject 5001-(b) (6) intensified resulting in bilateral below the knee amputations, and was reported late to the sponsor and reported late to the IRB, several months after the start of the event.

Reviewer's Comments: The protocol required that investigators report SAEs to the sponsor within 24 hours of learning of its occurrence. In the three cases above, the reports to sponsor were made within one week of the SAE. For Subjects 5001-(b) (6) and -(b) (6), the adverse events are correctly reported as SAEs in the data listings. The SAE for Subject 5001-(b) (6) is not included in the data listings because it occurred during the screening period and the subject was not enrolled in the study.

Most of the source records at the site documenting the ophthalmic assessments were inadequate. Specifically, for thirteen out of the fifteen subjects that were reviewed, they lacked one or more of the following: subject ID number, data of assessment, and signature or initials of the person completing the procedure. Monitoring reports at the site indicate that the monitor was aware of the deficiency and repeatedly requested that the site rectify the issue.

Reviewer's Comments: The ophthalmic records lacking a date or a subject ID are impossible to attribute to a specific subject on a specific assessment timepoint. The records lacking documentation of who performed the exam are impossible to verify as having been done by a qualified individual. Thus, the ophthalmic records at the site are unreliable.

In ten out of thirteen subjects, there were SAEs submitted to the Sponsor and listed in the data listings in which the site did not maintain documentation of the SAE submissions to the sponsor.

Reviewer's Comments: The records regarding the timing and confirmation of SAE reporting to the sponsor were obtained from the sponsor during the inspection. Dr. Roychowdhury failed to retain records required to reconstruct the conduct of the study at the site.

Overall survival data was verified with source records at the site for all subjects. No unreported adverse events were identified.

In a letter dated 2/11/2021, Dr. Roychowdhury acknowledged the described deficiencies identified during the inspection and described his corrective and preventative action (CAPA) plans.

Reviewer's Comments: The inspection identified several instances in which Dr. Roychowdhury failed to adhere to the protocol, failed to adequately supervise the study at the site, and failed to adequately retain records. There was no evidence of harm to subjects. Other than the ophthalmic safety assessments described previously, there was no evidence that the study data generated by the site was unreliable. The described CAPA plans are adequate.

2. Dr. Milind Javle (CI Site 5003)
1515 Holcombe Blvd Unit 426,
University of Texas, MD Anderson Cancer Center
Houston, TX 77030-4000
Inspection dates: December 7-11, 14, and 21, 2020

This investigator was inspected as an on-site surveillance inspection for Study CBGJ398X2204. This was the first FDA inspection for this investigator.

The enrollment logs inspected at the site were consistent with the data listings. At the time of the data cutoff, the investigator site had screened 34 subjects and enrolled 26. Subject 5003-(b) (6) was enrolled on (b) (6) and withdrew consent 2 days later. Seven subjects were screen failures: Subjects 5003-(b) (6) (b) (6), and (b) (6). Subject 5003-(b) (6) was not included in the data listings, however, signed informed consent before the data cutoff, on March 5, 2020; the subject was a screen failure. The records of all 26 enrolled subjects were reviewed at the site.

The inspection reviewed the subject source data for the 26 enrolled subjects and compared them to the data listings. The reviewed subject records included informed consent, medical records, concomitant medications, adverse events and SAEs, and imaging data. The inspection also reviewed study records including Form FDA 1572s, financial disclosures, on site protocol and amendments, monitoring and training activities, IRB communications, and investigational product shipping records.

There was no under reporting of adverse events, however, three serious adverse events in 2 subjects were not reported to the sponsor within the protocol required 24-hour time frame. Specifically Subject 5003-(b) (6) was hospitalized (b) (6) for abnormal liver function, Subject 5003-(b) (6) was hospitalized (b) (6) for abdominal pain, and again (b) (6) for abdominal pain. These SAEs were reported to the sponsor anywhere between 2 weeks to 7 months after the event.

Reviewer's Comments: The protocol required that investigators report SAEs to the sponsor within 24 hours of learning of its occurrence. In the first two instances above, the reports to sponsor were made within two weeks of the SAE. For Subject 5003-(b) (6)'s second hospitalization, the event was not reported for 7 months, however, it was related to the previous hospitalization, so it was not an unknown safety issue. All of the adverse events are correctly reported as SAEs in the data listings.

There were unreported protocol deviations, specifically, Subject 5003-(b) (6) had no pregnancy test on cycle 4 day 1 ((b) (6)), Subject 5003-(b) (6) had no pregnancy test on cycle 2, day 1 ((b) (6)) and cycle 3, day 1 ((b) (6)), and Subject 5003-(b) (6) had only abdomen and chest CT/MRI (no pelvis) at screening ((b) (6)). These protocol deviations were not in the data listings. The deviation for Subject 5003-(b) (6) was reported to the IRB on 4/15/2019, almost 4 years later.

Reviewer's Comments: None of the protocol deviations are reported in the data listings. They were either not reported or reported late to the IRB. There was no evidence of subsequent pregnancy for the subjects for whom protocol-required pregnancy tests were not performed. In the case of Subject 5003-(b) (6), the missing CT pelvis at screening would not have impacted efficacy endpoints because the subject had disease progression on the first follow-up assessment date.

There were 2 time periods where there was a lapse in IRB approval, specifically, from 06/04-11/2014 (6 days) and from 02/05-27/2020 (21 days). During these two lapses, the site did not enroll any new subjects.

Reviewer's Comments: During the lapse in IRB oversight, no subjects were enrolled in the study. It appears there was no subject harm due to these lapses and they were caught and eventually corrected.

There was a failure to obtain informed consent (IC) correctly, specifically, three subjects did not re-consent on IC version 8 (approved on 8/26/2015) and all had 2 follow visits and were not re consented. These were: Subject 5003-(b) (6) (signed original IC (b) (6)); version 8 not signed on follow up (b) (6) or (b) (6), Subject 5003-(b) (6) (signed original IC (b) (6)); version 8 not signed on follow up (b) (6) or (b) (6), Subject 5003-(b) (6) (signed original IC on (b) (6)); version 8 not signed on (b) (6) or (b) (6). The deviation for Subjects 5003-(b) (6) and 5003-(b) (6) were reported to the IRB as a violation 6/4/2019.

Reviewer's Comments: The changes in the updated informed consent were minor and likely would not affect a subject's decision to participate in the study, therefore, it does not appear that there was any subject harm due to the failure to reconsent subjects on an updated informed consent. Additionally, it does not affect data integrity and the issue was identified and corrected.

The primary endpoint was based on independent review of imaging. The inspection verified that the site correctly sent imaging studies to the central imaging entity ((b) (4)) according to the protocol. The inspection also reviewed source records and clinical notes to confirm clinical disease progression. No significant data discrepancies were identified between source records at the site and the submitted data listings. The ophthalmic exams and laboratory assessments for both hyper/hypophosphatemia and hyper/hypocalcemia were reviewed and confirmed to be performed according to protocol.

In a letter dated 1/4/20121, Dr. Javle acknowledged the described deficiencies identified during the inspection and described his CAPA plans.

Reviewer's Comments: The inspection identified several instances in which Dr. Jayle failed to adhere to the protocol, failed to ensure IRB oversight, and failed to correctly obtain informed consent. There was no evidence of harm to subjects and there was no evidence that the study data generated by the site was unreliable. The described CAPA plans are adequate.

3. QED Therapeutics, Inc. (Sponsor)
8000 Marina Blvd, Suite 400
Brisbane, CA 94005

Inspection Dates: December 11 – 21, 2020

The firm was inspected as an on-site surveillance inspection for Study CBGJ398X2204. This is the first FDA inspection for this Sponsor.

Records reviewed included informed consent template forms, site approvals, investigator qualifications, monitoring staff qualifications, monitoring reports, investigator 1572's, financial disclosure agreements, drug accountability documentation, corrective and preventative actions (CAPAs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARS), IND safety reporting, product labeling, data integrity and adherence to standard operating procedures (SOPs).

The sponsor submitted three reports of two SUSARs late to the FDA, specifically:

Table 3: SUSAR reports submitted late to FDA

Report	QED notification	Due date to FDA	Submission to FDA	Days Late
QED-2019-000023 initial Nausea, vomiting and GERD	10/15/2019	10/29/2019	11/29/2019	27
QED-2019-000023 FU1	11/7/2019	11/21/2019	11/29/2019	4
QED-2019-000022 FU1 Spontaneous penile erection/ curvature	11/1/2019	11/15/2019	11/27/2019	12

The company became aware of the issue on 11/21/2019 with QED-2019-000023 FU1 and conducted an impact assessment and identified the 2 additional SUSARs noted above. Since the initial issue was identified on November 21, 2019, no expedited safety reports (ESRs) have been reported late to FDA.

Reviewer's Comments: The Sponsor did not notify the FDA within the required 15 day reporting period for a SUSAR, 21 CFR 312.32 (c)(1). The reports to the sponsor were made within 4-21 days of the requirement, making it unlikely that the delays contributed to harm to subjects in terms of tracking SAEs related to the study drug. Their CAPA plan appears acceptable and there have been not late reports which required expedited reporting since November 21, 2019.

The inspection reviewed monitoring SOPs and all monitoring reports for sites 5001, 5003, 5011 and demonstrated that the site monitors did 100% source data verification for informed consent, eligibility criteria, SAEs, protocol deviations, endpoints, and IP verification. There were, however, multiple concerns with the monitoring process including: lack of documentation of monitor training, delayed finalization of monitoring reports, and delay in bringing noncompliant sites into compliance.

Reviewer's Comments:
The monitoring issues were not associated with any negative impacts on the study conduct or subject safety. The monitoring was overall adequate.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Review Division /Division Director/Lola Fashoyin-Aje, M.D.
Review Division /Project Manager/ Christina Leach
Review Division/Cross Discipline Team Lead/ Sandra Casek, MD
Review Division/Clinical Reviewer/ Lorraine Pelosof, MD

OSI/Office Director/Dave Burrow
OSI/DCCE/ Division Director/Ni Khin, M.D.
OSI/DCCE/Branch Chief/Kassa Ayalew, M.D., M.P.H.
OSI/DCCE/Acting Team Leader/Karen Bleich, M.D.
OSI/DCCE/GCP Reviewer/Michele Fedowitz, M.D.
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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.

/s/

MICHELE B FEDOWITZ
03/05/2021 04:24:31 PM

KAREN B BLEICH
03/05/2021 04:27:17 PM

KASSA AYALEW
03/06/2021 08:54:41 AM

Medical Officer's Review of NDA 214622
Ophthalmology Consultant

NDA 214622 Submission: 9/29/2020
Review completed: 1/25/2021

Name: Infigratinib

Sponsor: QED Therapeutics, Inc.

Pharmacologic Category: Kinase inhibitor of fibroblast growth factor receptor (FGFR)

Indications: the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by an FDA-approved test.

Requested: This is a new molecular entity (NME) original NDA submission that will likely be granted a priority review. DO3 requests your evaluation of the monitoring ophthalmologic plan and input on additional measures that could help detect/mitigate eye toxicity. Further specific questions and references from the NDA will be sent via email from the RPM.

From Table 5:Ocular AEs (≥10.0%) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	Monotherapy Safety Analyst Set	Primary Safety Analysis Set
Ocular Adverse Event	Day 90 Update	Day 90 Update
	N=356	N=108
Dry eye	85 (24%)	39 (36%)
Vision blurred	41 (11.5%)	23 (21%)

From Table 13:Summary of AESIs (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	Monotherapy Safety Analyst Set	Primary Safety Analysis Set
Adverse Event of Interest	Day 90 Update	Day 90 Update
	N=356	N=108
Eye disorder, including CSR/RPED	186 (52%)	76 (70%)
CSR/RPED	38 (11%)	18 (17%)

AESI=adverse event of special interest; CSR/RPED=central serous chorioretinopathy/retinal pigment epithelial detachment.

Table 14:Summary of AEs for the AESI of Eye Disorder (Including CSR/RPED) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set) Day 90 Update

	Monotherapy Safety Analyst Set	Primary Safety Analysis Set
	N=356	N=108
Adverse Event of Interest	186 (52%)	76 (70%)
SAE	3 (0.8%)	0
Led to study drug discontinuation	8 (2%)	3 (3%)
Led to dose reduction/interruption	41 (11.5%)	
Led to dose interruption	ND	12 (11%)
Led to dose adjustment	ND	8 (7%)
Led to concomitant medication or non-drug therapy	104 (29%)	46 (43%)
Outcome		
Not recovered/not resolved	111 (31%)	45 (42%)
Recovered/resolved	73 (20.5%)	29 (27%)
Unknown	2 (0.6%)	2 (2%)
Time to onset of any AE, days		
Mean (SD)	42.2 (47.28)	48.2 (49.57)
Median	23.0	24.5
Min, max	1.0, 313.0	1.0, 223.0

Table 15:AEs for the AESI of Eye Disorders (Excluding CSR/RPED) (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set) Day 90 Update

Adverse Event of Interest	Monotherapy Safety Analyst Set	Primary Safety Analysis Set
	N=356	N=108
Grouped PTs for eye disorders, excluding CSR/RPED terms	177 (49.7)	76 (70%)
Dry eye*	85 (24%)	39 (36%)
Vision blurred	41 (11.5%)	23 (21%)
Lacrimation increased*	23 (6.5%)	13 (12%)
Blepharitis	16 (4.5%)	12 (11%)
Punctate keratitis*	18 (5%)	10 (9%)
Conjunctivitis*	15 (4%)	2 (2%)
Keratitis*	15 (4%)	7 (6.5%)
Trichiasis	16 (4.5%)	12 (11%)
Visual impairment	14 (4%)	2 (2%)
Eye pain*	12 (3%)	5 (5%)
Ocular hyperaemia*	10 (3%)	5 (5%)
Cataract	10 (3%)	4 (4%)
Cataract nuclear	9 (2.5%)	8 (7%)
Keratopathy*	9 (2.5%)	1 (1%)
Photophobia*	9 (2.5%)	4 (4%)
Eye irritation*	7 (2%)	0
Growth of eyelashes	7 (2%)	7 (6.5%)
Madarosis	8 (2%)	5 (5%)

CSR/RPED=central serous chorioretinopathy/retinal pigment epithelial detachment;
* Dry eye, lacrimation increased, keratitis, hyperemia, photophobia, eye irritation likely the same events.

Table 16: Summary of AEs for the AESI of CSR/RPED (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set) Day 90 Update

	Monotherapy Safety Analyst Set	Primary Safety Analysis Set
	N=356	N=108
CSR/RPED [a]		
Any AE	38 (11%)	18 (17%)
SAE	0	0
Led to study drug discontinuation	2 (1%)	2 (2%)
Drug related	35 (10%)	17 (16%)
Led to dose reduction/interruption	12 (3%)	ND [c]
Led to dose interruption	ND	4 (4%)
Led to dose adjustment	ND	3 (3%)
Led to concomitant medication or nondrug therapy	2 (1%)	1 (1%)
Outcome [b]		
Not recovered/not resolved	26 (7%)	13 (12%)
Recovered/resolved	12 (3%)	5 (5%)
Time to onset of any AE, days		
Mean (SD)	72.1 (99.53)	78.3 (94.38)
Median	26.0	39.0
Min, max	8.0, 461.0	9.0, 378.0

AE=adverse event; AESI=adverse event of special interest; CSR/RPED=central serous chorioretinopathy/retinal pigment epithelial detachment; max=maximum; min=minimum; ND=not done for the data set; NE=not estimable; PT=preferred term; SAE=serious adverse event; SD=standard deviation.

[a] Subset of CSR/RPED PTs from the eye disorder system organ class are listed in Section 13.3 of the ISS SAP.

[b] Reflecting outcome of the last AE based on AE start day; if multiple AEs on the same day, then the worst outcome. Both 'recovering/resolving' and 'not recovered/not resolved' are considered as 'not recovered/not resolved'; and both 'recovered/resolved' and 'recovered/resolved with sequelae' are considered as 'recovered/resolved'.

Reviewer's Comments:

1. Dry Eye occurred in approximately one third of patients. The terms recorded as dry eye, lacrimation increased, keratitis, keratopathy, conjunctivitis, hyperemia, photophobia, eye irritation are likely to be alternative names for an equivalent event.

2. CSR/RPED was reported in approximately 15% of patients.

3. Blurred vision may be due to either dry eye or CSR/RPED.

4. CTCAE Class 1, 2, 3 and 4 as defined are not considered reflective of the severity of ocular events and are not recommended to be used for ocular events.

Labeling Recommendations:

Reviewer's Comments: *The following labeling changes are recommended:*

2.3 Dose Modification for Adverse Reactions

(b) (4)

WARNINGS AND PRECAUTIONS
5.1 Ocular Disorder

(b) (4) Retinal Pigment Epithelial Detachment ((b) (4) RPED)

[TRADENAME] can cause (b) (4) RPED, which may cause symptoms such as blurred vision. (b) (4)
(b) (4)

Among 351 patients who received [TRADENAME] across clinical trials, (b) (4) RPED occurred in 11% of patients The median time to first onset of (b) (4) RPED was 26 days.

Perform a comprehensive ophthalmic examination including OCT prior to initiation of [TRADENAME], at 1 month, at 3 months, and then every 3 months thereafter during treatment. Refer patients for ophthalmic evaluation urgently for onset of visual symptoms, and follow-up every 3 weeks until resolution or discontinuation of [TRADENAME].

(b) (4)

Dry Eye

Among 351 patients who received [TRADENAME] across clinical trials, dry eye occurred in (b) (4) % of patientsTreat patients with ocular demulcents as needed.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Ocular (b) (4) *[see Warnings and Precautions (0)]*
- Hyperphosphatemia *[see Warnings and Precautions **(Error! Reference source not found.)**]*

Clinical Trials Experience

…

Table 1: Adverse Reactions (≥15%) in Patients Receiving [TRADENAME] in Study CBGJ398X2204

	[TRADENAME] N=108	
Adverse Reaction	**All Grades (%)**	**Grades (b) (4) (%)**
Eye disorders		
Dry eye [e]	44	*[f]
Vision blurred	21	*[f]

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 4.03).

a (b) (4)

b

c

d

e Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.

f Severity of eye disorders is not represented by CTCAE.

g (b) (4)

Reviewer's Comments:

1. CTCAE does not provide an accurate representation of the severity of ocular events.

2. Eyelash changes demonstrate both growth and reduction of growth. These may be consistent with normal eyelash turnover.

Summary Comments:

Dry eye symptoms and Retinal Pigment Epithelial Detachment were common ocular adverse events following the use of Infigratinib. The CTCAE does not provide an accurate assessment of severity of ocular events and is not recommended to be used for ocular events in clinical trials or labeling of

ocular adverse events. Labeling revisions are recommended to the proposed labeling. The labeling revisions are described in this review.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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.

/s/

WILEY A CHAMBERS
01/25/2021 08:55:41 AM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214622
Submission Number	0001
Submission Date	9/30/2020
Date Consult Received	10/26/2020
Drug Name	Infigratinib phosphate (BGJ398, BBP-831)
Indication	For the treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA approved test
Therapeutic dose	125 mg orally once daily (QD) for 3 weeks followed by 1 week off therapy, in 28-day cycles; take on an empty stomach
Clinical Division	Division of Oncology (DO) 3

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

This review responds to your consult dated 10/26/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT reviews under IND 104187 dated 10/18/19 and 7/22/20 in DARRTS;
- Sponsor's cardiac safety report CBGJ398X 2101 (Submission 0002);
- Sponsor's cardiac safety report CBGJ398X 2204 (Submission 0001);
- Sponsor's clinical study ECG report QED-PKPD-001 (Submission 0001);
- Sponsor's nonclinical overview (Submission 0002);
- Sponsor's proposed label (Submission 0001); and
- Highlights of Clinical Pharmacology and Cardiac Safety (Submission 0292; IND 104187)

1 SUMMARY

No large mean increases in the QTc interval (i.e., >20 msec) were observed in this QT assessment of 125 mg/day infigratinib (3-week-on-1 week-off dosing regimen). Without a positive control or a large exposure margin, we are reluctant to conclude a lack of an effect (ICH E14 Q&A (R3) 6.1). This QT assessment does not cover the increases in infigratinib exposure with concomitant use of strong CYP3A4 inhibitors — there were concentration-dependent effects in the in vitro hERG study and in clinical studies.

The effect of infigratinib was evaluated in studies CBGJ398X2101 and CBGJ398X2204. The study treatment that provided the highest exposure was 125 mg/day, 3-weeks-on-1-week-off; this is also the proposed therapeutic dose. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that

infigratinib is associated with large mean increases on the QTc interval – see Table 1 for overall result. The findings of this analysis are further supported by the available by-timepoint analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Treatment	Infigratinib concentration (ng/mL)	ΔQTCF (msec)	90% CI (msec)
Infigratinib 125 mg/day, Day 15, CSF (N=47; CBGJ398X2101)	171.4	3.1	(1.8, 4.3)
Infigratinib 125 mg/day, Day 15, FMI III (N=29; CBGJ398X2204)	200.8	3.4	(2.0, 4.8)
Infigratinib 125 mg/day, reported Cmax*	295.3	4.4	(2.5, 6.3)

** Geometric mean Cmax on Day 15, mostly with FMI III (CBGJ398X2204 PK report)*

Infigratinib is predominantly metabolized by CYP3A4. A strong inhibitor of CYP3A4 (itraconazole) increased the AUC and Cmax of infigratinib by 7-fold and 2.5-fold, respectively. Mild and moderately hepatically impaired patients showed a two-fold increase in AUC and Cmax. Food increases the exposure of infigratinib by 2-fold compared to the fasted state. Age, sex, race, body weight showed no effect. The effect of renal impairment, renal dialysis in end-stage renal disease, or severe hepatic impairment on infigratinib exposure is unknown.

1.1 Responses to Questions Posed by Sponsor

Not applicable.

1.2 Comments to the Review Division

The QT assessment does not provide full coverage for the proposed therapeutic exposure (see Table 1 above). We do not have major concerns with therapeutic exposure because the nonclinical studies provided a reasonable safety margin for the parent drug and major metabolites, and the predictions of QTc effect based on clinical PK/ECG data were consistently below 10 msec under various scenarios. Extrapolation of the conclusion to a higher dose or exposure (e.g., with drug interaction) is not appropriate given the narrow exposure range in this QT assessment, a concentration-dependent effect in the in vitro hERG study, and the observation of a trend for increased QTc interval with increased concentrations in the pooled dataset.

2 RECOMMENDATIONS

2.1 Additional Studies

Not applicable.

2.2 Proposed Label

Below are proposed edits to the label submitted to Submission 0001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) as a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology (b) (4) At (b) (4) (b) (4) the recommended dosing regimen (b) (4) Infigratinib does not result in a large (b) (4) mean increase (i.e. >20 msec) (b) (4) in the QTc interval. The QT effect of infigratinib at higher exposures associated with CYP3A4 inhibition has not been studied.
Reviewer's Comment: (b) (4) *We propose to report the target effect size of this QT assessment (i.e. 20 msec) according to ICH E14 Q&A 6.1.* *We do not agree with reporting* (b) (4) *in the product label because* (b) (4) .

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Infigratinib phosphate (BGJ398, BBP-831) is indicated for the treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA approved test. The recommended dose of infigratinib is 125 mg (administered as one 100 mg capsule and one 25 mg capsule) orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Capsules should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Previously the IRT concluded that it appeared reasonable to use studies CBGJ398X2101 and CBGJ398X2204 to evaluate whether infigratinib treatment is associated with large mean increases (i.e., 20 msec) in the QTc interval (IRT review in DARRTS dated 10/18/2019 and 7/22/20). The adequacy of the cardiac safety analysis remained a review issue depending on the exposure coverage.

Study CBGJ398X2101 was a multi-center, open-label, Phase I dose escalation study in patients with advanced solid malignancies. The study involved two formulations of infigratinib (the clinical service form, CSF, and the final market image [FMI] I). FMI I was only used in a subgroup of patients on 125 mg/day, 3 weeks-on-1- week-off. In the dose escalation phase (5-150 mg daily dose), duplicated 12-lead ECGs were acquired with matching PK at predose and at 0.5, 1, 2, 3, 4, and 8 hours postdose on Cycle (C) 1 Days (D) 1, 15, and 28; in the expansion cohorts (125 mg daily, continuous or 3 weeks-on-1- week-off), ECG data were collected at pre-dose, and 2 and 4 hours postdose on C1D1 and D15. Additional PK/ECG were collected predose on multiple other days.

Study CBGJ398X2204 is an ongoing multicenter, open-label, 3-cohort, Phase 2 study in advanced or metastatic cholangiocarcinoma patients with FGFR genetic alterations. Patients received oral infigratinib 125 mg QD using a 3-weeks on, 1-week off schedule

for each 28-day treatment cycle with formulations FMI I (n=51), FMI III (n=48), and FMI IV (the to-be-marketed formulation, n=9). Triplicate ECGs were collected at predose, 2 and 4 hours postdose on C1 D1 and D15, predose and 2 hour postdose on C1 D2 and D8, and predose on multiple other days. In the actual submission, only 3 patients provided PK/ECG data at 4 hour dose.

3.1.2 Nonclinical Safety Pharmacology Assessments

To evaluate potential effects on cardiac conduction, infigratinib was tested for its effect on human ether-à-go-go related gene (hERG) potassium ion channel current in human embryonic kidney 293 (HEK293) cells. A concentration-dependent inhibition of the hERG current was observed from 1 to 10 μM, ranging from 28.1% to 93.8%. The calculated IC50 value for hERG current inhibition of 2.0 μM (1.1 μg/mL), was approximately 104x. The Cmax is 330.3 ng/mL (0.3303 μg/mL) at the clinical recommended dose of 125 mg QD infigratinib.

BHS697 inhibited hERG current in a concentration dependent manner from 0.3 to 9.6 μM, ranging from 10% to 100%. The calculated IC50 for BHS697-related hERG current inhibition was 1.2 μM (0.637 μg/mL). The Cmax of BHS697 is 51.67 ng/mL (0.05167 μg/mL) at the clinical recommended dose of 125 mg QD infigratinib. Based on mean plasma unbound BHS697 of 1.3% the projected unbound plasma Cmax is 0.0006717 μg/mL, thus providing a 948x exposure margin (0.637 μg/mL/0.0006717 μg/mL) at the recommended clinical dose of 125 mg QD infigratinib.

CQM157 inhibited hERG current in a concentration dependent manner from 0.3 to 10 μM, ranging from 1.8% to 95.7%. The calculated IC50 for CQM157-related hERG current inhibition was 2.7 μM (1.25 μg/mL). The Cmax of CQM157 is 19.97 ng/mL (0.01997 μg/mL) at the clinical recommended dose of 125 mg QD infigratinib. Based on mean plasma unbound CQM157 of 0.5% the projected unbound plasma Cmax is 0.0000998 μg/mL, thus providing a 12,000x exposure margin (1.25 μg/mL /0.0000998 μg/mL) at the recommended clinical dose of 125 mg QD infigratinib.

Reviewer's comment: *It is not known if the in vitro hERG studies were conducted under best practice (see S7b Q&As).*

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for infigratinib was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *Sponsor's by-time analyses does not suggest meaningful effect of infigratinib on QTcF. Sponsor's results are similar to reviewer's analysis results. Please see section 4.3 or details.*

3.2.1.1 Assay Sensitivity

Not applicable

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, HR (<45 or >100 beats/min), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *Sponsor's results are similar to reviewer's outlier analysis. Please see section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor evaluated the relationship between ΔQTcF and plasma concentration of infigratinib, or in separate models its metabolites BHS697 and CQM157 (and BQR917 in the CBGJ398X2101 study) using a linear mixed-effects modeling approach. The default model included plasma concentration, time, adjusted baseline, and random subject effect on the intercept and slope.

Study CBGJ398X2204: The sponsor mentions that there were 295 observations from 71 patients in this study. According to them this provided inadequate sampling and too small a sample size for PK-PD analysis, and therefore they conducted PK-PD analysis using the pooled data from studies 2101 and 2204.

Study CBGJ398X2101 and pooled analysis from studies CBGJ398X2101 and CBGJ398X2204: When plasma concentrations of infigratinib or the metabolites was used as the exposure covariate, all the upper bound of 90% CI on the predicted QTc effect were below 10 msec. The sponsor did not report parameter estimate for the slope.

Reviewer's comments: *The reviewer's analysis are in agreement with the sponsor's analysis in that the predicted QTc effect at the therapeutic exposure are below 10 msec.*

It is observed that the Cmax steady state values of infigratinib are different across various scenarios (i.e., studies) when looking at the same dosing schedule of 125 mg once a day for 3 weeks on and 1 week off. In study CBGJ398X2101, median Tmax of the parent drug was 4 hours postdose and Cmax was 214 ng/mL on Cycle 1 Day 15 (n=35). In study CBGJ398X2204, the average Cmax was 330.3 ng/mL and median Tmax was 6 hours on Cycle 1 Day 15 (n=11). This difference in Cmax is not likely caused by formulation differences because relative bioavailability studies showed comparable exposure of infigratinib for CSF and FMI III. The difference in Cmax values seems to be attributable to the different disease state patient populations in the two studies. The higher Cmax in cholangiocarcinoma patients may be due to more vascularity (e.g., easier conveyance, and possibly, transfer of body fluids) in these patients compared to patients with solid tumors.

3.2.4 Cardiac Safety Analysis

In study CBGJ398X2101, there were 17 (8%) subjects who experienced a cardiac-related TEAE. Subject (b) (6) had a fatal cardiac arrest. None of the AEs were significant ventricular arrhythmias.

In study CBGJ398X2204, a total of 23 subjects (21%) had at least 1 cardiac-related TEAE as shown in the Sponsor's Table 51 below. No subjects discontinued study drug due to an AE of cardiac disorder. Two subjects (2%) had at least 1 Grade 3 event (tachycardia and peripheral swelling) and no subjects had a Grade 4 event. One subject had a serious AE of Grade 3 tachycardia.

Table 51: Treatment Emergent Adverse Events of Cardiac Disorder by Sub-category and Preferred Term (Interim Analysis Set 2 for Cohort 1)

	By Formulation			
Sub-category/Preferred Term	FMI I (N=51) n (%)	FMI III (N=48) n (%)	FMI IV (N=9) n (%)	All Subjects (N=108) n (%)
Cardiac failure	6 (11.8)	12 (25.0)	1 (11.1)	19 (17.6)
Oedema peripheral	4 (7.8)	9 (18.8)	1 (11.1)	14 (13.0)
Peripheral swelling	1 (2.0)	2 (4.2)	0	3 (2.8)
Oedema	1 (2.0)	0	1 (11.1)	2 (1.9)
Left ventricular dysfunction	0	1 (2.1)	0	1 (0.9)
Arrhythmia related investigations, signs, and symptoms	3 (5.9)	2 (4.2)	0	5 (4.6)
Palpitations	1 (2.0)	2 (4.2)	0	3 (2.8)
Bradycardia	1 (2.0)	0	0	1 (0.9)
Tachycardia	1 (2.0)	0	0	1 (0.9)

Abbreviations: FMI=final market image.
Source: Table 14.3.1.14.1

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Review of the ECG waveforms submitted to the ECG warehouse showed that 25% (1198 out of 4842) and 11% (1122 out of 9885) ECG waveforms were potentially digitized in studies CBGJ398X2204 and CBGJ398X2101, respectively. There were 57 (47%) and 82 (40%) subjects that have at least 1 digitized ECG in studies CBGJ398X2204 and CBGJ398X2101, respectively. Without the original digital ECG waveforms, it cannot be determined whether the redigitization process may have increased the variance in the QT, which would have reduced the power to detect a treatment effect (*Stockbridge, N., J Electrocardiol 2005; 38, 319-20*). Thus, while the rest of quality metrics looked overall acceptable, the potential impact of measures from potentially digitized ECG waveforms was also assessed in FDA sensitivity analyses.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG. Time points beyond the 6th cycle and time points with

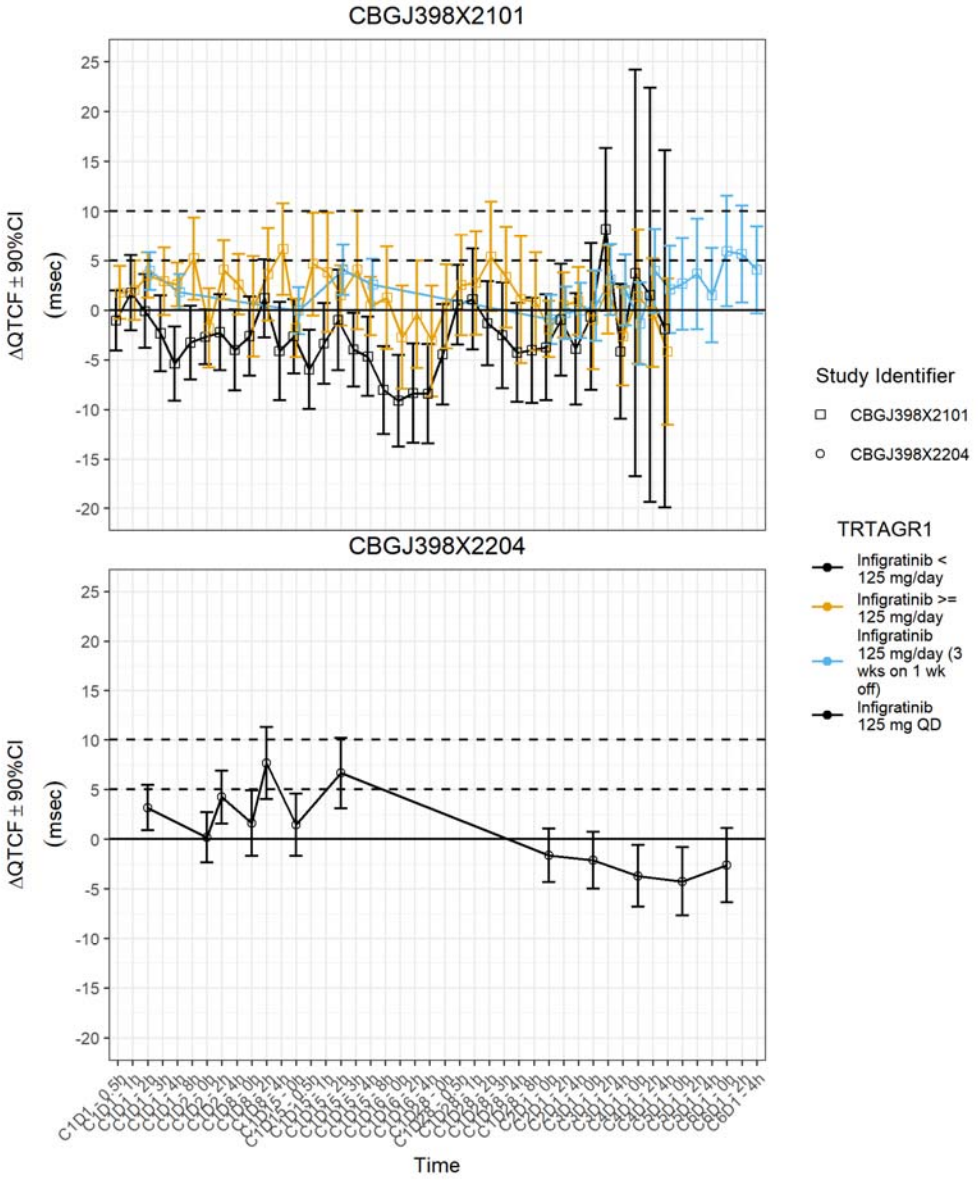
less than 10 observations remining in individual treatment groups are not shown in the figures and tables in this sections.

The statistical reviewer evaluated the ΔQTcF effect using parametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTc for different treatment groups. Sensitivity analyses excluding subjects with digitized ECG waveforms showed similar results and did not change interpretation of the overall study findings.

Figure 1: Mean and 90% CI of ΔQTcF Time Course (unadjusted CIs).



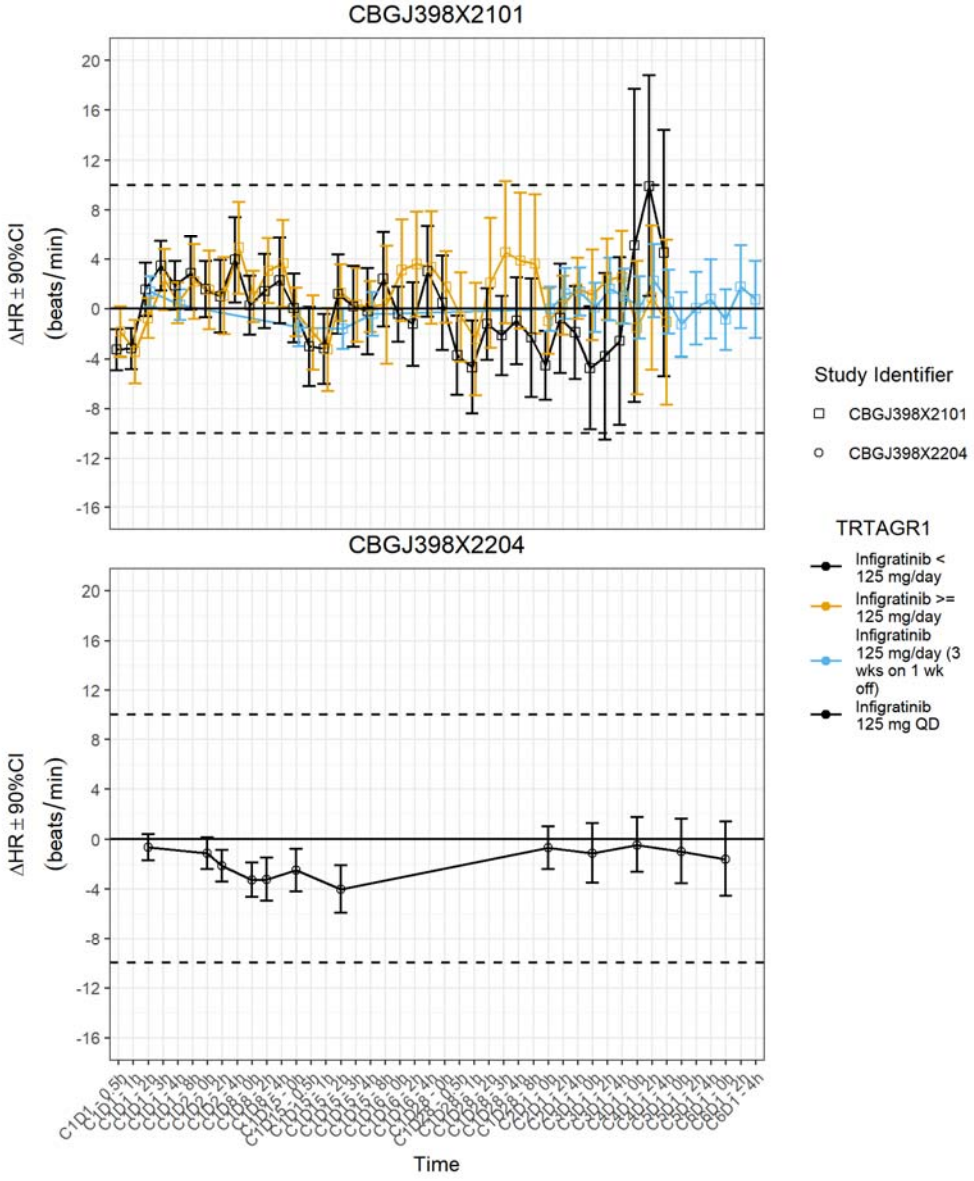
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

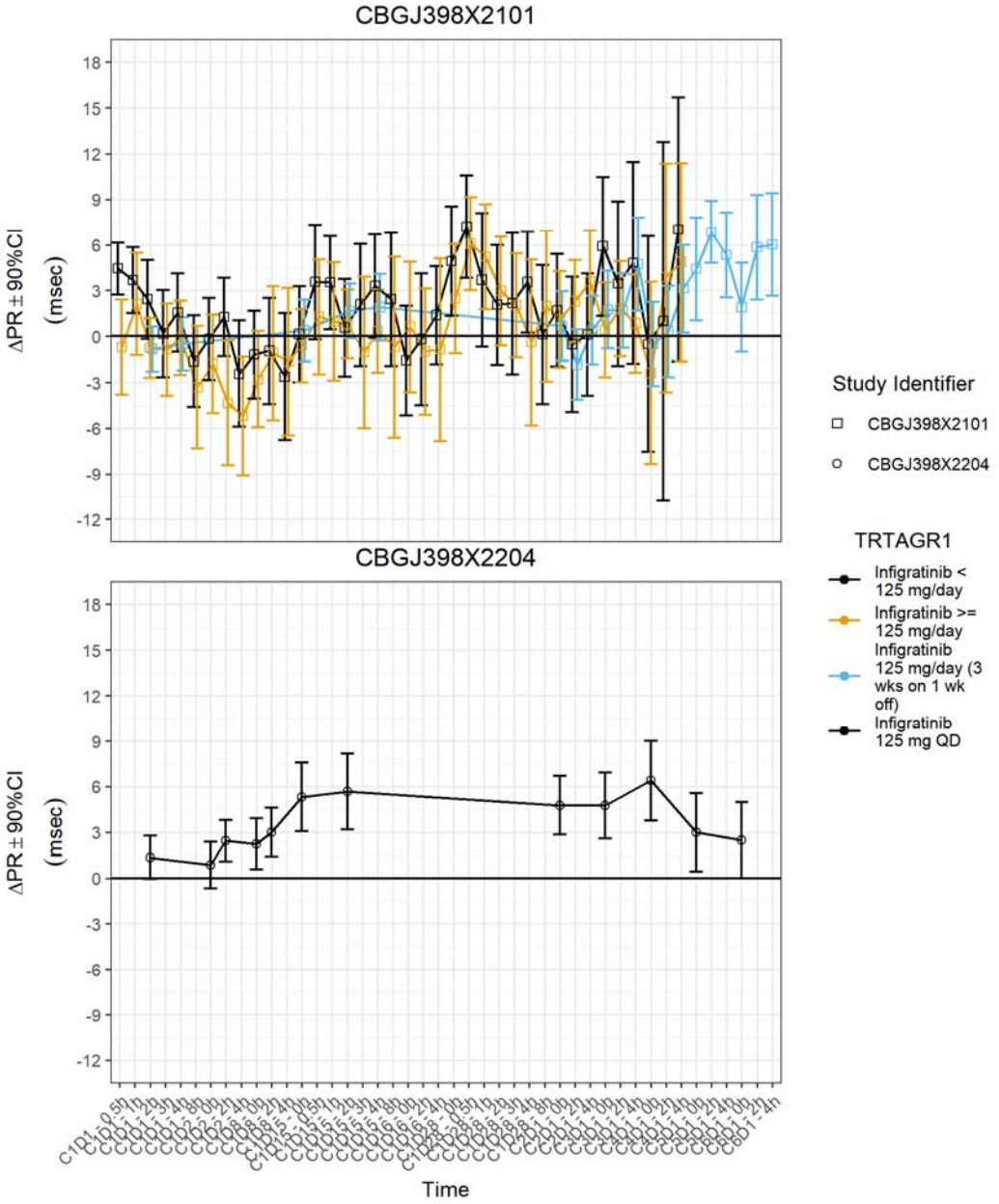
Figure 2: Mean and 90% CI of ΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

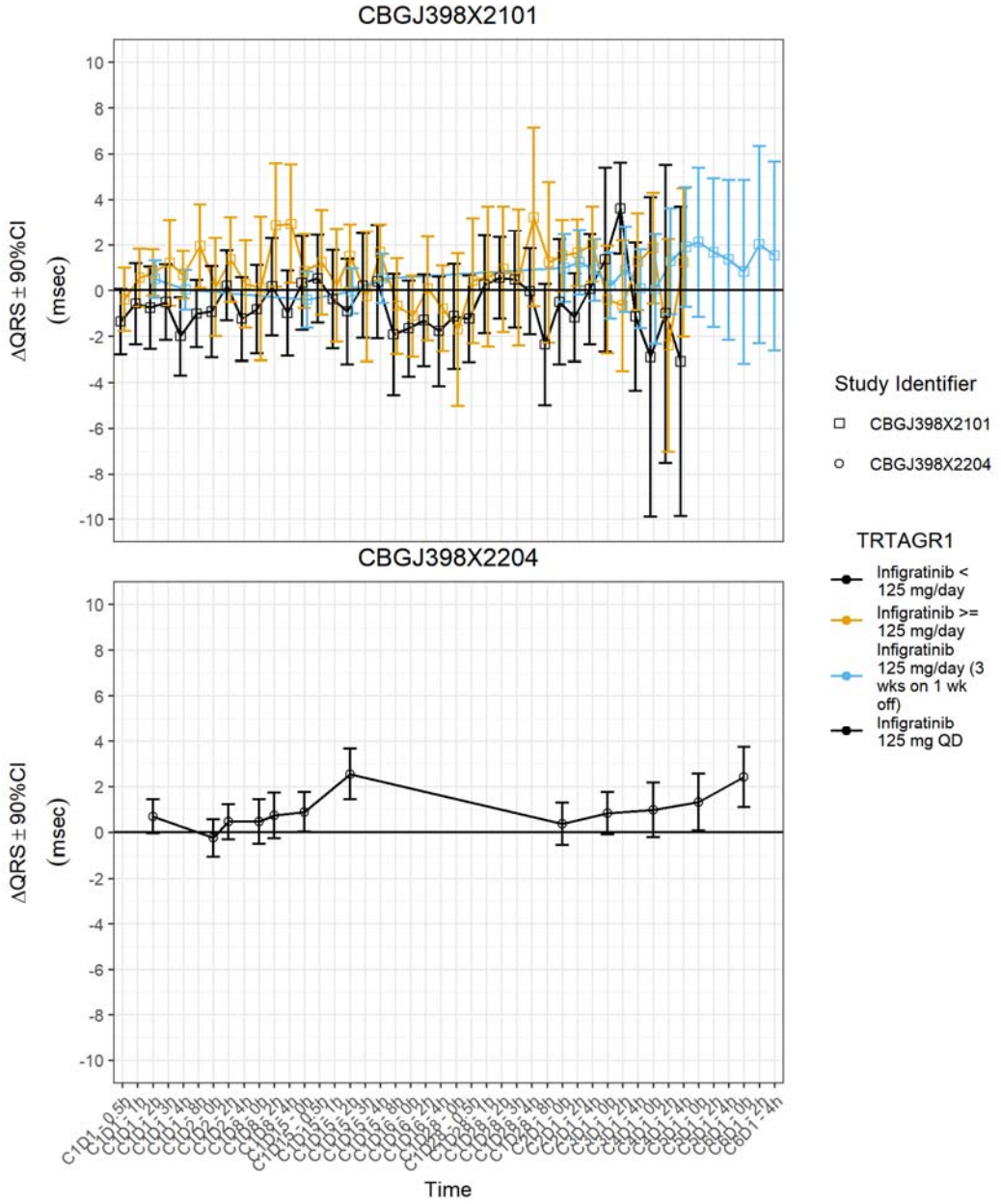
Figure 3: Mean and 90% CI of ΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and included both scheduled and unscheduled ECGs.

4.4.1 QTc

Table 2 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 msec, between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec with or without a change from baseline greater than 60 msec. There was one subject in the infigratinib 125 mg/day (3 wks on 1 wk off) arm experienced QTcF above 500 msec with change from baseline below 60 msec at one timepoint.

Table 2: Categorical Analysis for QTcF

Treatment Group	Total (N)		Value <= 450 msec		450 < Value <= 480 msec		480 < Value <= 500 msec		Value > 500 & Δ < 60 msec	
	# Subj	# Obs	# Subj	# Obs	# Subj	# Obs	# Subj	# Obs	# Subj	# Obs
Study CBGJ398X2101										
Infigratinib < 125 mg/day	29	858	27 (93.1%)	844 (98.4%)	2 (6.9%)	14 (1.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infigratinib >= 125 mg/day	63	982	59 (93.7%)	960 (97.8%)	4 (6.3%)	22 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infigratinib 125 mg/day (3 wks on 1 wk off)	116	1608	100 (86.2%)	1502 (93.4%)	12 (10.3%)	96 (6.0%)	3 (2.6%)	9 (0.6%)	1 (0.9%)	1 (0.1%)
Study CBGJ398X2204										
Infigratinib 125 mg QD (3 wks on 1 wk off)	117	1308	98 (83.8%)	1273 (97.3%)	18 (15.4%)	34 (2.6%)	1 (0.9%)	1 (0.1%)	0 (0%)	0 (0%)

Table 3 lists the categorical analysis results for ΔQTcF. There was 1 subject who had QTcF change from baseline above 60 msec at 2 timepoints after receiving infigratinib 125 mg QD.

Table 3: Categorical Analysis for ΔQTcF

Treatment Group	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study CBGJ398X2101								
Infigratin b < 125 mg/day	29	858	26 (89.7%)	845 (98.5%)	3 (10.3%)	13 (1.5%)	0 (0%)	0 (0%)
Infigratin b >= 125 mg/day	63	982	58 (92.1%)	973 (99.1%)	5 (7.9%)	9 (0.9%)	0 (0%)	0 (0%)
Infigratin b 125 mg/day (3 wks on 1 wk off)	116	1608	93 (80.2%)	1536 (95.5%)	23 (19.8%)	72 (4.5%)	0 (0%)	0 (0%)
Study CBGJ398X2204								
Infigratin b 125 mg QD (3 wks on 1 wk off)	117	1308	97 (82.9%)	1254 (95.9%)	19 (16.2%)	52 (4.0%)	1 (0.9%)	2 (0.2%)

4.4.2 HR

Table 4 lists the categorical analysis results for HR. There were 7 to 16% subjects experienced HR above 100 bpm after receiving infigratinib 125 mg/day on 3 wks on 1 wk off schedule. There were 21% of subjects experienced HR above 100 bpm after receiving infigratinib 125 mg/day on continuous schedule.

Table 4: Categorical Analysis for HR

Treatment Group	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study CBGJ398X2101						
Infigratinib < 125 mg/day	29	858	22 (75.9%)	825 (96.2%)	7 (24.1%)	33 (3.8%)
Infigratinib >= 125 mg/day	63	982	50 (79.4%)	948 (96.5%)	13 (20.6%)	34 (3.5%)
Infigratin b 125 mg/day (3 wks on 1 wk off)	116	1608	98 (84.5%)	1574 (97.9%)	18 (15.5%)	34 (2.1%)
Study CBGJ398X2204						
Infigratin b 125 mg QD (3 wks on 1 wk off)	117	1308	109 (93.2%)	1297 (99.2%)	8 (6.8%)	11 (0.8%)

4.4.3 PR

Table 5 lists the categorical analysis results for PR. There were two subjects experienced PR above 220 msec with corresponding change from baseline above 25% after receiving infigratinib 125 mg QD.

Table 5: Categorical Analysis for PR

Treatment Group	Total (N)		Value <= 220 msec		Value > 220 msec & Δ < 25%		Value > 220 msec & Δ >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study CBGJ398X2101								
Infigratin b < 125 mg/day	29	858	27 (93.1%)	845 (98.5%)	2 (6.9%)	13 (1.5%)	0 (0%)	0 (0%)
Infigratin b >= 125 mg/day	63	982	60 (95.2%)	963 (98.1%)	3 (4.8%)	19 (1.9%)	0 (0%)	0 (0%)
Infigratin b 125 mg/day (3 wks on 1 wk off)	114	1588	103 (90.4%)	1490 (93.8%)	11 (9.6%)	98 (6.2%)	0 (0%)	0 (0%)
Study CBGJ398X2204								
Infigratin b 125 mg QD (3 wks on 1 wk off)	116	1300	109 (94.0%)	1250 (96.2%)	5 (4.3%)	46 (3.5%)	2 (1.7%)	4 (0.3%)

4.4.4 QRS

Table 6 lists the categorical analysis results for QRS. There was one subject in 125 mg/day (3 wks on 1 wk off) arm experienced QRS > 120 msec with corresponding change from baseline above 25% at multiple time points.

Table 6: Categorical Analysis for QRS

Treatment Group	Total (N)		Value <= 120 msec		Value > 120 msec & Δ < 25%		Value > 120 msec & Δ >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study CBGJ398X2101								
Infigratin b < 125 mg/day	29	858	29 (100.0%)	858 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infigratin b >= 125 mg/day	63	982	60 (95.2%)	979 (99.7%)	3 (4.8%)	3 (0.3%)	0 (0%)	0 (0%)
Infigratin b 125 mg/day (3 wks on 1 wk off)	116	1608	106 (91.4%)	1429 (88.9%)	9 (7.8%)	150 (9.3%)	1 (0.9%)	29 (1.8%)

Treatment Group	Total (N)		Value <= 120 msec		Value > 120 msec & Δ < 25%		Value > 120 msec & Δ >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Study CBGJ398X2204								
Infigratin b 125 mg QD (3 wks on 1 wk off)	117	1308	112 (95.7%)	1258 (96.2%)	5 (4.3%)	50 (3.8%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK in the first cycle. The initial assessment for model assumptions were based on study CBGJ398X2101 because it provided more intensive PK/ECG sampling schedule as compared to study CBGJ398X2204. The primary analysis was conducted with pooled dataset including studies CBGJ398X2101 and CBGJ398X2204 because study CBGJ398X2204 provided a wider exposure range and the data appear appropriate for pooling. Sensitivity analyses were conducted with all available time-matched PK/ECG data or with dataset excluding digitized ECGs.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis on PK/ECG data from study CBGJ398X2101: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc and 3) presence of non-linear relationship.

- Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes.
- Figure 5 evaluates the time-course of drug-concentration and ΔQTc for the 100 mg QD, 125 mg QD, and 125 mg/day 3-weeks-on-1-week-off groups. These dose groups were selected for the plot because of relatively large sample size. The overlapping PK profiles on Days 15 and 28 for the 100 mg QD and 125 mg QD groups suggested that steady state is almost reached on Day 15. Despite of clear accumulation in drug exposure, ΔQTc profiles highly overlap on different days and are relatively flat within each study day. Overall, the data do not suggest significant hysteresis. According to the clinical study report, median Tmax is 3-4 hours postdose at these dose levels. Geometric Cmax values were comparable in the PK/ECG dataset and in the full PK dataset.
- Figure 6 (Left) shows the relationship between drug concentration and ΔQTc and supports the use of a linear model. When the linear model (ΔQTcF ~ 1 + CONC + centered baseline, random effect on the intercept and slope) was applied to the data, the goodness-of-fit plot is shown in Figure 6 (Right). The model does not suggest a statistically significant slope for the concentration-QTc relationship and the predictions do not suggest large mean effect at the observed geometric mean Cmax for the 125 mg QD dose level (171.4 ng/mL, Day 15, N=47).

Figure 5: Time course of drug concentration and QTc in study CBGJ398X2101

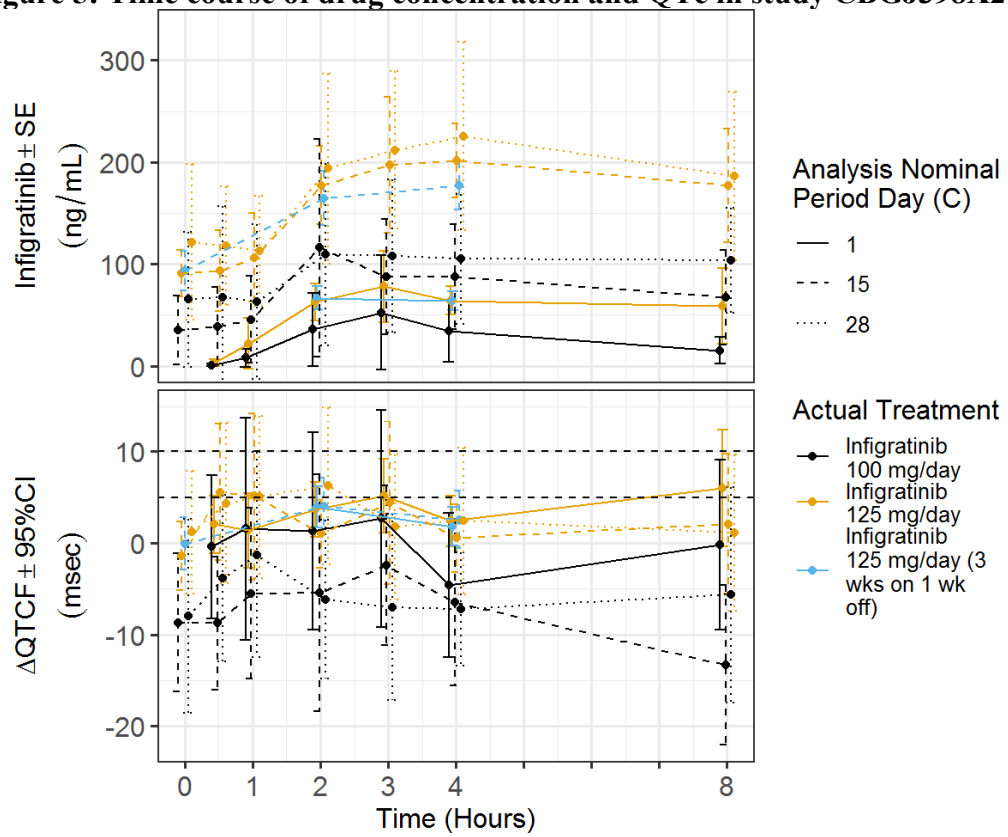
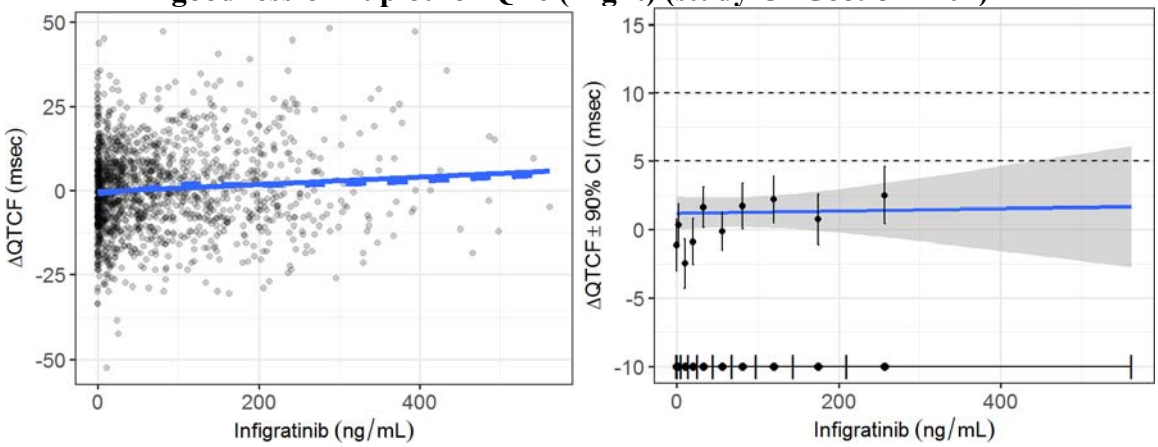


Figure 6: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) (study CBGJ398X2101)



In the primary analysis, PK/ECG data from study CBGJ398X2204 was examined and pooled with study CBGJ398X2101 for concentration-QTc analysis.

- Figure 7 shows the time course of drug concentration and QTc in study CBGJ398X2204. According to the pharmacokinetic report of study CBGJ398X2204, the average Cmax of at the 125 mg daily dose on Day 15 is 330.3 ng/mL (geometric mean: 295.3 ng/mL; n=10 on FMI III, n=1 on FMI IV) and median Tmax was 6 hours. Overall, therapeutic exposure is approximately 50% higher than maximum exposure in the pooled PK/ECG dataset (295.1 ng/mL vs. 200.1 ng/mL).

- Figure 8 suggested that pooled PK/ECG data from the two studies generally support the use of linear model and the two studies appears to show similar linear exposure-response relationship.
- The linear model suggested a positive concentration-QTc relationship; however, the predictions from this model does not suggest large mean increases on the QTc interval at the observed geometric mean Cmax at the 125 mg QD dose in the two studies. The goodness-of-fit plot is shown in Figure 9: and predictions are provided in Table 1.

Figure 7: Time course of drug concentration and QTc in study CBGJ398X2204

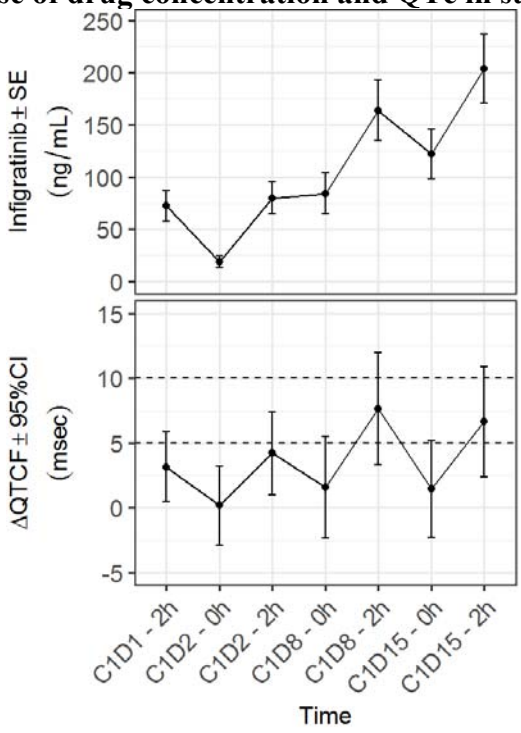


Figure 8: Assessment of linearity of concentration-QTc relationship (studies CBGJ398X2101 and CBGJ398X2204)

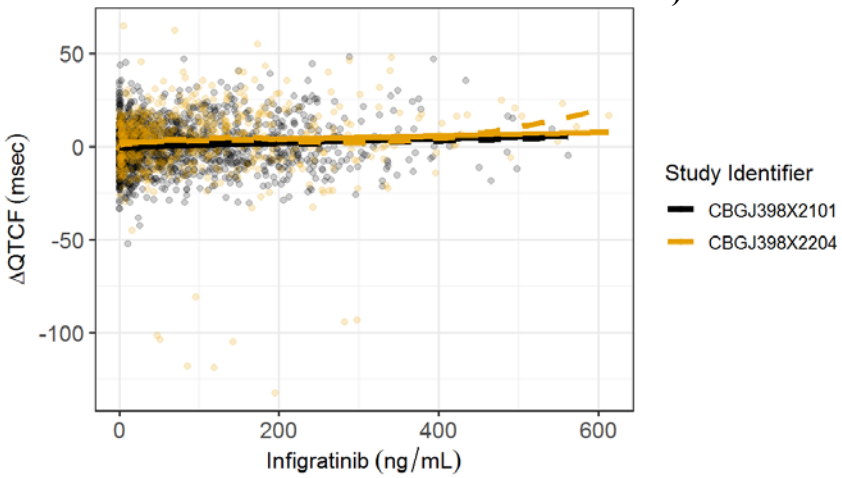
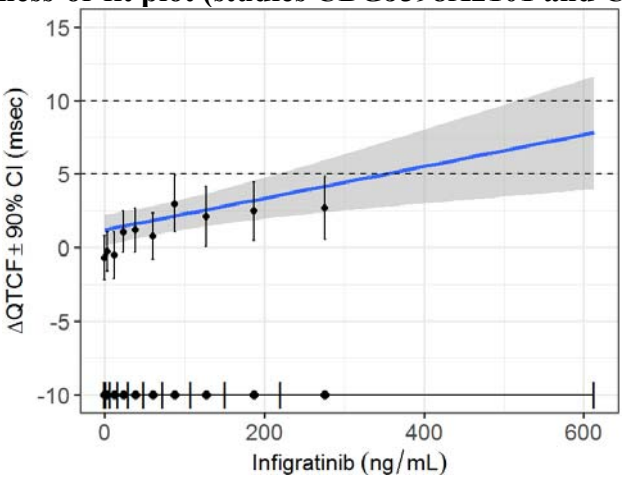


Figure 9: Goodness-of-fit plot (studies CBGJ398X2101 and CBGJ398X2204)



In the concentration-QTc analysis dataset, all the ΔQTcF values <-55 msec were derived from digitized ECG data. In a sensitivity analysis excluding patients with digitized ECGs, similar results were obtained in study CBGJ398X2101 alone or in the pooled dataset. The addition of PK/ECG data beyond the first cycle also generated similar results as compared to the primary analysis.

In the full PK dataset from study CBGJ398X2204, Cmax of the two major metabolites, BHS697 and CQM157, were reported to be 52 ng/mL (63%) (geometric mean: 43.5 ng/mL) and 20 ng/mL (78%) (geometric mean: 15.0 ng/mL), respectively. This QT assessment provided adequate exposure coverage for CQM157 (geometric mean Cmax 16 ng/mL in study CBGJ398X2101, 125 mg/day 3 wks on 1 wk off, Day 15). Therapeutic Cmax for BHS697 is approximately 33% higher than that was observed in this QT assessment (32.1 ng/mL, observed on Day 15 in study CBGJ398X2204). In the concentration-QTc analyses using metabolites as the exposure covariate, the upper bound of 90% confidence of predicted effect at the reported Cmax values were below 10 msec.

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.

/s/

RAMAN K BAWEJA
01/06/2021 05:23:08 PM

NAN ZHENG
01/06/2021 05:35:18 PM

YU YI HSU
01/06/2021 05:40:14 PM

DALONG HUANG
01/06/2021 05:43:56 PM

MICHAEL Y LI
01/07/2021 08:11:18 AM

JOSE VICENTE RUIZ
01/07/2021 08:49:07 AM

CHRISTINE E GARNETT
01/07/2021 09:18:07 AM