NDA 214622

ACCELERATED APPROVAL

QED Therapeutics, Inc.
Attention: Amanda Roodhouse
8000 Marina Boulevard, Suite 400
Brisbane CA 94005

Dear Ms. Roodhouse:

Please refer to your new drug application (NDA) dated September 29, 2020, received September 29, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Truseltiq (infigratinib) capsules, 25mg and 100mg, for oral use.

This new drug application provides for the use of Truseltiq (infigratinib) capsules, for oral use, for the treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangement as detected by an FDA approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and text for the Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL*

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Standard for Content of Labeling Technical Qs and As.[2]
The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your May 20, 2021, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Truseltiq (infigratinib) capsules shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86ºF).

ADVISORY COMMITTEE

Your application for Truseltiq was not referred to an FDA advisory committee because this drug is not the first in its class and no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of infigratinib for the proposed indication.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 24, 2021. This requirement, along with required completion dates, is listed below.

4067-1 Submit the final progression-free survival (as assessed by blinded independent review) analysis and interim overall survival analysis at the time of final progression-free survival analysis, including datasets from a randomized clinical trial comparing infigratinib to chemotherapy to verify and describe the clinical benefit of infigratinib in patients with advanced or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. Ensure that racial and ethnic minority subjects are adequately represented in the trial population, at a minimum, proportional

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

to the prevalence of FGFR2 alterations in these subgroups in the US population.

Final Protocol Submission:	10/2018
Trial Completion:	12/2026
Final Report Submission:	06/2027

Submit clinical protocols to your IND 104187 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for cholangiocarcinoma for this application. The necessary studies are impossible or highly impracticable because the incidence of cholangiocarcinoma is 0.36/100,000 in patients younger than 20 years of age. In addition, FGFR-altered cholangiocarcinoma represent only a subset (15-20%) of all cholangiocarcinomas and therefore pediatric studies are impossible to conduct in this indication.

We are waiving the pediatric study requirement for ages 0 to 28 days because necessary studies are impossible or highly impracticable. This is because FGFR mutations in pediatric tumors seldom occur before one year of age.

We are deferring submission of your pediatric study for ages 29 days and older for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing

study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4067-2 Submit the final study report for the "Phase 1b/2, Multicenter, Open-label Study of Oral Infigratinib in Pediatric Subjects With Advanced Solid Tumors (Phase 1b) and in Subjects With Recurrent or Refractory Low-grade Gliomas (Phase 2) Harboring Selected FGFR1, FGFR2, or FGFR3 Alterations" study to further characterize the safety, pharmacokinetics, and anti-tumor activity of infigratinib for pediatric patients 29 days of age or older with advanced or metastatic solid tumors harboring FGFR2 gene alterations.

Draft Protocol Submission:	11/2021
Final Protocol Submission:	01/2022
Study Completion:	03/2028
Final Report Submission:	08/2028

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 104187, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of potential drug interaction when infigratinib is co-administered with transporter substrates.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4067-3 Conduct an in vitro study to evaluate the potential of drug-interaction of the major metabolites (BHS697, CQM157, and BQR197), on the transporters MATE and OCT. Evaluate the overall in vivo potential of infigratinib and metabolites as inhibitors on the transporters in accordance with the FDA Guidance for Industry titled "In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	12/2021
Study Completion:	06/2022
Final Report Submission:	12/2022

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of hyperphosphatemia and eye disorders in patients administered infigratinib and to assess a signal of serious risk of elevated drug levels to determine appropriate dose adjustment when infigratinib is used concomitantly with moderate CYP3A4, P-gp and BCRP inhibitors and BCRP substrates .

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4067-4 Conduct a clinical trial to further characterize the serious adverse reactions of hyperphosphatemia and eye disorders in patients with first-line or refractory cholangiocarcinoma harboring an FGFR2 fusion or other rearrangement receiving alternate dosage(s) regimens of infigratinib. Characterize all serious adverse events including hyperphosphatemia and eye disorders, dose reductions, interruptions, and discontinuations due to

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

serious adverse events. Compare clinical efficacy and safety descriptively across concurrently-enrolled, parallel cohorts evaluating the approved infigratinib dosage and an alternate dosage regimen. Include sparse PK samples for exposure-response analyses for efficacy and safety and conduct exploratory PK/PD analysis using serum phosphate levels. Ensure that racial and ethnic minority subjects are adequately represented in the trial population, at a minimum, proportional to the prevalence of FGFR2 alterations in these subgroups in the US population.

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2021
Final Protocol Submission:	12/2021
Study Completion:	06/2025
Final Report Submission:	12/2025

4067-5 Conduct a drug interaction study in patients to evaluate the effect of a moderate CYP3A4 inhibitor on the pharmacokinetics of infigratinib and its major metabolites to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when infigratinib is administered concomitantly with moderate CYP3A4 inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	01/2022
Trial Completion:	02/2027
Final Report Submission:	08/2027

4067-6 Conduct a drug interaction study to evaluate the effect of a P-gp inhibitor on the pharmacokinetics of infigratinib and its major metabolites to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when infigratinib is administered concomitantly with P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	06/2022
Study Completion:	02/2023
Final Report Submission:	08/2023

4067-7 Conduct a drug interaction study to evaluate the effect of a BCRP inhibitor on the pharmacokinetics of infigratinib and its major metabolites to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when infigratinib is administered concomitantly with BCRP inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled " Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2022
Final Protocol Submission:	06/2022
Study Completion:	02/2023
Final Report Submission:	08/2023

4067-8 Conduct a drug interaction study in patients to evaluate the effect of multiple-dose infigratinib on the pharmacokinetics of a BCRP substrate to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when infigratinib is administered concomitantly with BCRP substrates. Design and conduct the study in accordance with the FDA Guidance for Industry titled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	01/2022
Study Completion:	02/2027
Final Report Submission:	08/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit clinical protocol(s) to your IND 104187 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4067-9 Conduct a drug interaction study in patients to evaluate the effect of a moderate CYP3A4 inducer on the pharmacokinetics of infigratinib and its major metabolites to assess the magnitude of decreased drug exposure and determine appropriate dosage recommendations when infigratinib is administered concomitantly with moderate CYP3A4 inducers. Design and conduct the study in accordance with the FDA Guidance for Industry titled " Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2021
Final Protocol Submission:	01/2022
Study Completion:	02/2027
Final Report Submission:	08/2027

4067-10 Submit results from exploratory next generation sequencing analyses of longitudinal tumor and/or blood samples acquired at baseline, on treatment and at the time of progression from patients treated with infigratinib during a randomized Phase 3 trial in patients with cholangiocarcinoma with FGFR2 fusions/rearrangements aimed at identifying potential mechanisms of primary and acquired resistance to infigratinib. Include a discussion of the results in the context of the available published literature. The results of this study may inform product labelling.

The timetable you submitted on May 24, 2021, states that you will conduct this study according to the following schedule:

Study Completion:	12/2027
Final Report Submission:	06/2028

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 104187 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

If you have any questions, contact Christina Leach, PharmD, Regulatory Health Project Manager, at 240-402-6571 or christina.leach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
    - Prescribing Information
    - Patient Package Insert
- Carton and Container Labeling

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

PAUL G KLUETZ
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