

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214622Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

FDA review was conducted in conjunction with other regulatory authorities under a regular ORBIS. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies (Health Canada and Therapeutic Goods Administration).

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	214622
Priority or Standard	Priority
Submit Date(s)	September 29, 2020
Received Date(s)	September 29, 2020
PDUFA Goal Date	May 29, 2021
Division/Office	OOD/DO3
Review Completion Date	Please check electronic date stamp
Established Name	Infigratinib
Trade Name	Truseltiq
Pharmacologic Class	FGFR Inhibitor
Code name	BGJ398
Applicant	QED Therapeutics, Inc.
Formulation(s)	Oral capsule
Dosing Regimen	125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles
Applicant Proposed Indication(s)/Population(s)	The treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other rearrangement as detected by an FDA approved test.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For 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.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation.....	11
Additional Reviewers of Application	11
Glossary	13
1 Executive Summary.....	16
1.1. Product Introduction	16
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	16
1.3. Benefit-Risk Assessment (BRA)	18
1.4. Patient Experience Data	26
2 Therapeutic Context	27
2.1. Analysis of Condition	27
2.2. Analysis of Current Treatment Options	30
3 Regulatory Background.....	37
3.1. U.S. Regulatory Actions and Marketing History	37
3.2. Summary of Presubmission/Submission Regulatory Activity.....	37
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	39
4.1. Office of Scientific Investigations (OSI)	39
4.2. Product Quality.....	39
4.3. Clinical Microbiology	40
4.4. Devices and Companion Diagnostic Issues	40
5 Nonclinical Pharmacology/Toxicology	41
5.1. Executive Summary	41
5.2. Referenced NDAs, BLAs, DMFs	43
5.3. Pharmacology	43
5.4. ADME/PK	47
5.5. Toxicology.....	49
5.5.1. General Toxicology	49

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

5.5.2. Genetic Toxicology	65
5.5.3. Carcinogenicity	66
5.5.4. Reproductive and Developmental Toxicology	66
5.5.5. Other Toxicology Studies	74
6 Clinical Pharmacology	76
6.1. Executive Summary	76
6.1.1. Recommendations.....	76
6.1.2. Post-Marketing Requirements and Commitments	78
6.2. Summary of Clinical Pharmacology Assessment	82
6.2.1. Pharmacology and Clinical Pharmacokinetics.....	82
6.2.2. General Dosing and Therapeutic Individualization	85
6.2.2.1. General Dosing	85
6.2.2.2. Therapeutic Individualization	91
6.2.2.3. Outstanding Issues	97
6.3. Comprehensive Clinical Pharmacology Review.....	97
6.3.1. General Pharmacology and Pharmacokinetic Characteristics.....	97
6.3.2. Clinical Pharmacology Questions.....	105
7 Sources of Clinical Data.....	114
7.1. Table of Clinical Studies	114
8 Statistical and Clinical Evaluation.....	125
8.1. Review of Relevant Individual Trials Used to Support Efficacy	125
8.1.1. Study CBGJ398X2204.....	125
8.1.2. Study Results	134
8.1.3. Integrated Review of Effectiveness	156
8.1.4. Assessment of Efficacy Across Trials.....	156
8.1.5. Integrated Assessment of Effectiveness	157
8.2. Review of Safety	158
8.2.1. Safety Review Approach.....	159
8.2.2. Review of the Safety Database	160
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments	168

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

8.2.4. Safety Results	171
8.2.5. Analysis of Submission-Specific Safety Issues	188
8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability	190
8.2.7. Safety Analyses by Demographic Subgroups	190
8.2.8. Specific Safety Studies/Clinical Trials.....	195
8.2.9. Additional Safety Explorations.....	195
8.2.10. Safety in the Postmarket Setting	197
8.2.11. Integrated Assessment of Safety	197
SUMMARY AND CONCLUSIONS	200
8.3. Statistical Issues.....	200
8.4. Conclusions and Recommendations	200
9 Advisory Committee Meeting and Other External Consultations	203
10 Pediatrics	204
11 Labeling Recommendations.....	205
12 Risk Evaluation and Mitigation Strategies (REMS)	207
13 Postmarketing Requirements and Commitment	208
14 Division Director (DHOT) (NME ONLY)	211
15 Division Director (OCP)	212
16 Division Director (OB)	213
17 Division Director (Clinical).....	214
18 Office Director (or designated signatory authority)	215
19 Appendices	216
19.1. References	216
19.2. Financial Disclosure.....	220
19.3. Nonclinical Pharmacology/Toxicology.....	221
19.4. OCP Appendices (Technical documents supporting OCP recommendations)	222
19.4.1. Summary of Bioanalytical Method Validation and Performance.....	222

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

19.4.2.	Formulation Bridging.....	224
19.4.3.	Population PK Analysis	228
19.4.4.	Exposure-Response Analysis	244
19.4.5.	Pharmacogenomic Exploratory Analysis.....	253
19.5.	Additional Safety Analyses Conducted by FDA.....	256

Table of Tables

Table 1: Summary of Currently Available Treatments for Patients with Previously Treated Cholangiocarcinoma with FGFR2 fusion.....	31
Table 2: Key FDA Interactions for IND 104,187	37
Table 3: Infigratinib Inhibitory Activity Using a 126-Kinase-Platform Assay	43
Table 4: Infigratinib Inhibitory Activity in a Cell-Based ELISA Assay	44
Table 5: In Vitro Binding of Infigratinib and Metabolites BHS697 and CQM157 to FGFRs	44
Table 6: Anti-proliferative Activity of Infigratinib in Human Cell Lines.....	44
Table 7. Summary of Clinical Pharmacology Post-Marketing Requirements and Commitments	78
Table 8. Subject number stratified by last dose at the occurrence of BOR.	89
Table 9. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with moderate renal impairment (Test) to healthy subjects with normal renal function (reference).	93
Table 10. TEAEs leading to dose modification stratified by renal function categories.	93
Table 11. Simulated potency adjusted AUC _{activity} (μM*h) of infigratinib and BHS697, CQM157 for each renal impairment category in Study CBGJ398X2204 at 125 mg, 100 mg, and 75 mg.....	93
Table 12. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with mild hepatic impairment (Child Pugh A, Test) to healthy subjects with normal function (reference).	95
Table 13. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with moderate hepatic impairment (Child Pugh B, Test) to healthy subjects with normal function (reference).	96
Table 14. TEAEs leading to dose modification stratified by hepatic function categories.	96
Table 15. Simulated potency adjusted AUC _{activity} (μM*h) of infigratinib and BHS697, CQM157 for each renal impairment category in Study CBGJ398X2204 at 125 mg, 100 mg, and 75 mg.....	96
Table 16: Summary of Clinical Pharmacology Characteristics for Infigratinib	97
Table 17. NCA estimated PK parameters of infigratinib and active metabolites BHS697, CQM197 based on individual PK ^a estimates in patients with cholangiocarcinoma in Study CBGJ398X2204.	104
Table 18. Geometric Mean (%CV) Exposure of Infigratinib and Active Metabolites in the labeling.	105
Table 19. PK model predicted infigratinib AUC at steady state in the presence or absence of weak CYP3A4 inhibitors or inducers in Study CBGJ398X2204, assuming a 125-mg dose.	112
Table 20: Tabular Listing of All Clinical Studies.....	115
Table 21: Study CBGJ398X2204 SAP Amendments Summary	131
Table 22: Study CBGJ398X2204 Protocol Amendments	131
Table 23: Subject Disposition (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1).....	135
Table 24: CSR Reportable Protocol Deviations (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	136

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 25: Subject Demographics and Baseline Disease Characteristics (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	137
Table 26: Treatment Compliance (Study CBGJ398X2204)	141
Table 27: ATC Classes of Concomitant Conditions Taken by ≥15% of All Subjects (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	142
Table 28: Summary of Phosphate-binders (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	143
Table 29: Primary Endpoint of Overall Response Rate Assessed by BICR (Study CBGJ398X2204)	144
Table 30: ORR and DOR results by BICR and Investigator Assessment (N = 108)	146
Table 31: Concordance between BICR and Investigator assessed ORR	147
Table 32: Summary of Efficacy Results by BICR and Investigator (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	148
Table 33: Secondary Endpoint of Progression-free Survival (Study CBGJ398X2204 Interim Analysis Set 2)	151
Table 34: Overall Survival (Study CBGJ398X2204)	152
Table 35: PK Assessment (Study CBGJ398X2204)	155
Table 36: Exposure to Infigratinib (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)	161
Table 37: Subject Demographics (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)	162
Table 38: Baseline Disease Characteristics (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)	164
Table 39: Prior Antineoplastic Medications Taken by ≥5.0% of All Subjects (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)	166
Table 40: Primary Reasons for Death (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	171
Table 41: Serious Treatment Emergent Adverse Events That Occurred in >1 Subject by System Organ Class and Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	173
Table 42: Subject Disposition (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	174
Table 43: Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class/Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	175
Table 44: Treatment Emergent Adverse Events Leading to Dose Interruption in >2 Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	177
Table 45: Treatment Emergent Adverse Events Leading to Dose Adjustment in >2 Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	177
Table 46: Treatment Emergent Adverse Events Occurring in ≥10% of All Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	179
Table 47: Adverse Reactions (≥15%) in Patients Receiving Infigratinib in Study CBGJ398X2204	180

Table 48: Select Laboratory Abnormalities ($\geq 10\%$) Worsening from Baseline in Patients Receiving Infigratinib in Study CBGJ398X2204 (Interim Analysis Set 2 for Cohort 1)	183
Table 49 - All Grade laboratory abnormalities occurring in $\geq 10\%$ of patients	184
Table 50: QT, QTcF, and QTcB Outlier Values (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1: Subjects with Both Baseline and Postbaseline ECG Assessment)	186
Table 51: Overall Summary of Treatment-Emergent Adverse Events by Subgroup (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	191
Table 52: Treatment Emergent Adverse Events Occurring in $\geq 10\%$ of All Subjects by Preferred Term and Subgroup (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)	192
Table 53: Summary of Significant Labeling Changes	205
Table 54. Summary of bioanalytical method performance in infigratinib clinical studies.	222
Table 55. Summary of dose normalized descriptive PK by formulations, based on 5 healthy volunteer studies CBGJ398X2103, CBGJ398A2104, CBGJ398A2105, CBGJ398A2106, QBGJ398-109.	226
Table 56. Descriptive statistics of dose normalized $AUC_{activity}$ ($\mu M \cdot h/mg$) by formulations across healthy volunteer studies.	227
Table 57. Summary of simulated geometric mean (CV%) of infigratinib C_{max} and overall $AUC_{activity}$ following oral administration of infigratinib 125 mg (FMI-I, FMI-III and FMI-IV) on C1D1 and C1D15.	227
Table 58. Studies Included for Population PK Analysis.	229
Table 59. Summary of Baseline Demographic Characteristics and Laboratory Values in the Dataset.	232
Table 60. Number of Samples for Population PK Analysis in Interim Dataset 2 (March 2020 Cutoff) Stratified by Analyte.	233
Table 61. Parameter Estimates and SE from Final Infigratinib Population PK Model.	233
Table 62. Parameter Estimates and SE from Final BHS697 Population PK Model.	234
Table 63. Parameter Estimates and SE from Final CQM157 Population PK Model.	235
Table 64. Ratio of AUC Geomean Relative to Normal Hepatic/renal Function for Each Organ Impairment Category in Study 2204.	237
Table 65. Geometric Mean of Simulated Exposures at 125, 100, and 75 mg by Hepatic Impairment Category in Study 2204.	238
Table 66. Geometric Mean of Simulated Exposures at 125, 100, and 75 mg by Renal Impairment Category in Study 2204.	238
Table 67 Geometric Mean of Simulated AUC_{0-24h} Activity and Infigratinib C_{max} at 50, 75, 100, 125 mg by Organ Impairment Category in Study 2204.	240
Table 68. Studies Included for E-R Analyses.	245
Table 69. Summary of Baseline Demographic Characteristics in the Dataset by Last Dose.	246
Table 70. Summary of Baseline Demographic Characteristics from Patients with Pharmacokinetic observations in the Dataset by Study.	250
Table 71: Distribution of FGFR2 Fusions or other Rearrangements per Local and/or Central Testing (N=108)	254

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 72: FGFR2 Fusions and other Rearrangements in Study CBGJ398X2204 (N=106)	255
Table 73: BICR-Assessed Responses in Patients with FGFR2 Fusions or other Rearrangements in Study CBGJ398X2204 (N=108)	256

Table of Figures

Figure 1: Infigratinib Antitumor Efficacy in a PDX Mice Model with Cholangiocarcinoma	45
Figure 2: Infigratinib Antitumor Activity in CTG-0997 Cholangiocarcinoma PDX Mice.....	45
Figure 3: Western Blot Analysis of FRS2 Phosphorylation (pFRS2) and MAPK Activation in RT112 Tumor Xenografts	46
Figure 4. Tumor Response with Treatment Exposure.	88
Figure 5. Model predicted (90%) probability of best overall response versus potent adjusted $AUC_{activity}$ (nM*h) for infigratinib, BHS697, and CQM157 with observed data overlaid.	89
Figure 6. Kaplan-Meier plot of probability of hyperphosphatemia versus time, by quartile of potency adjusted $AUC_{activity}$ (nM*h).	90
Figure 7. Kaplan-Meier plot of probability of eye disorders (excluding CST/RPED) versus time, by quartile of potency adjusted $AUC_{activity}$ (nM*h).	90
Figure 8: CBGJ398X2204 Study Design.....	126
Figure 9: Subgroup Analyses of Overall Response Rate Assessed by BICR (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1).....	145
Figure 10: Waterfall Plot of Maximum Percent Reduction in Tumor Burden with Best Response Assessment by BICR (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1).....	150
Figure 11: Number of Subjects Exposed to Infigratinib in This Safety Evaluation	159
Figure 12. VPC for Infigratinib PPK Model in Double-log Scale, Stratified by Profile Type.	236
Figure 13. VPC for BHS697 PPK Model in Double-log Scale, Stratified by Profile Type.....	236
Figure 14. Overall activity AUC_{0-24h} in Mild (B1, B2) Hepatic Impairment by Simulated Doses of 125, 100, and 75 mg compared to Normal Hepatic Function.....	239
Figure 15. Overall activity AUC_{0-24h} in Renal Impairment by Simulated Doses of 125, 100, and 75 mg compared to Normal Renal Function.	239
Figure 16. Simulated Overall Activity AUC_{0-24h} by Organ Impairment Categories at 50, 75, 100, and 125 mg.	241
Figure 17. Model-predicted Probability of Overall Response versus Exposures Overlaid with Observed Data.	247
Figure 18. Week 8 Response Rate Versus Early Exposure Overlaid with Observed Data.	248
Figure 19. Probability of PFS by Exposure Quartiles.....	249
Figure 20. Hazard Ratio of Significant Covariates for Final Hyperphosphatemia Model.	252
Figure 21. Predicted Probability of Hyperphosphatemia at 50, 75, 100, and 125 mg.	253

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Christina Leach
Pharmacology/Toxicology Reviewer(s)	Denali (Dubravka) Kufrin
Pharmacology/Toxicology Team Leader(s)	Matthew Thompson
Office of Clinical Pharmacology (OCP) Reviewer(s)	DCPII: Lili Pan DPM: Ye Xiong Genomics: Oluseyi Adeniyi
Office of Clinical Pharmacology (OCP) Team Leader(s)	DCPII: Jeanne Fourie Zirkelbach DPM: Jiang Liu Genomics: Rosane Charlab Orbach
Clinical Reviewer	Lorraine Pelosof
Clinical Team Leader	Sandra J. Casak
Safety Team Analyst	Peter Schotland
Statistical Reviewer	Abhishek Bhattacharjee
Statistical Team Leader	Joyce Cheng
Associate Director for Safety (ADS)	Abhilasha Nair RPM: Stacie Woods
Associate Director for Labeling (ADL)	Ann Marie Trentacosti, Barbara Scepura
Cross-Disciplinary Team Leader	Sandra J. Casak
Division Director (DHOT)	John Leighton
Division Director (OCP)	NAM Atiqur Rahman
Division Director (OB)	Shenghui Tang
Division Director (OOD)	'Lola Fashoyin-Aje
Office Director (or designated signatory authority)	Paul Kluetz

Additional Reviewers of Application

OPQ	<u>RBPM</u> : Anita Brown <u>Drug Product</u> : Rajiv Agarwal, ATL: Xing Wang, BC: Anamitro Banerjee <u>Drug Substance</u> : Soumya Mitra, BC: Ali Al Hakim <u>OPMA</u> : Diane Goll, BC: Rakhi Shah
------------	---

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	<u>Biopharmaceutics</u> : Gerlie Gieser, TL: Banu Zolnik, BC: Angelica Dorantes
OPDP	Emily Dvorsky, TL: Susannah O'Donnell
OCP	QT/IRT: Nan Zheng, Girish Bende PBPK: Xinyuan Zhang, Yuching Yang
OSI	Michele Fedowitz, TL: Karen Bleich
OSE/DEPI	Steven Bird
OSE/DMEPA	Janine Stewart, TL: Ashleigh Lowery
OSE/DRISK	Brad Moriyama, TL: Naomi Boston
OSE/DPV	Connie Cheng, TL: Afrouz Nayernama, Peter Waldron
CDRH	Debu Chatterjee, BC: Soma Ghosh
DMPP (Patient Labeling)	Jessica Chung, TL: Barbara Fuller
Other (Ophthalmology Consult)	Wiley Chambers

OPQ=Office of Pharmaceutical Quality

TL= Team Lead

BC= Branch Chief

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

CDRH= Center for Devices and Radiological Health

DMPP= Division of Medical Policy Programs

Project Orbis #32 - Health Canada (HC; Canada) Review team	
Director BMORS	
Clinical Manager (Oncology Division 2)	
Project Management	
Lead Clinical Reviewer	
Non-clinical and Clin PK reviewer	
Chemistry and Manufacturing Reviewer	
Biopharmaceutics	

Project Orbis # 32 - Therapeutic Goods Administration (TGA; Australia) Review team	
Clinical Reviewer and Decision Delegate	
Clinical Team Lead	

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
BICR	blinded independent central review
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRA	Benefit-Risk Assessment
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
ClinRO	clinical reported outcome
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSR/RPED	central serous retinopathy/retinal pigment epithelium detachment
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DDI	drug-drug interaction
DEPI	Division of Epidemiology
DLT	dose-limiting toxicity
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

DOR	duration of response
DRISK	Division of Risk Management
ECG	electrocardiogram
eCTD	electronic common technical document
E-R	exposure-response
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FMI	Final Market Image
FGFR	fibroblast growth factor receptor
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NTRK	neurotrophic tyrosine receptor kinase
ObsRO	observer reported outcome
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OR	overall response
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PerfO	performance outcome
PFS	progression-free survival
PI	prescribing information

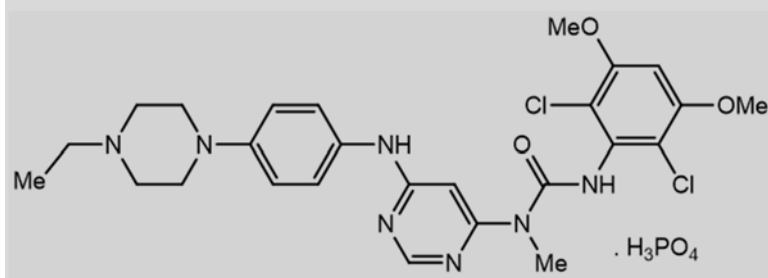
NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
WT	wild type

1 Executive Summary

1.1. Product Introduction

Infigratinib (previously called BGJ398 and BBP-831) is small molecule kinase inhibitor that is an ATP-competitive inhibitor of the fibroblast growth receptors (FGFRs) 1, 2, and 3. The chemical name is 3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethylpiperazin-1-yl) phenylamino] pyrimidin-4-yl}-1-methylurea phosphate (1:1). The chemical structure of infigratinib phosphate is as follows:



Infigratinib phosphate (infigratinib) is supplied as 25 mg and 100 mg hard gelatin capsules for oral administration. The inactive ingredients include lactose monohydrate, microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate, and colloidal silicon dioxide.

The proposed recommended dosage for infigratinib is 125 mg (one 100 mg capsule and one 25 mg capsule) administered orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Treatment is continued until disease progression or intolerable toxicity.

Truseltiq (infigratinib) is a new molecular entity and has not been previously marketed.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team agrees that the NDA for Truseltiq (infigratinib) capsules meets the statutory standards for approval under 21 CFR 314, Subpart H (accelerated approval) for the following indication:

TRUSELTIQ is indicated 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.

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 a confirmatory trial(s).

This approval recommendation is primarily based on safety and efficacy results of a single trial, Study CBGJ398X2204 (also referred to as Study 2204; NCT02150967). Study 2204 is an open label, non-randomized, multi-cohort trial that evaluated the efficacy of infigratinib in 108 patients with locally advanced unresectable or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement, whose disease had progressed on or after at least 1 prior therapy (Cohort 1). The safety of infigratinib is also supported by data from an additional 253 patients treated with infigratinib as a single agent in other clinical trials.

Study 2204 demonstrated a clinically meaningful and durable overall response rate (ORR) in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 gene fusion or rearrangement, a serious and life-threatening disease. Although pemigatinib is approved for use in the indicated population, it was granted accelerated approval and as such there remains an unmet medical need for treatments for the indicated population. In the studied population of 108 patients with FGFR2 gene fusion/rearrangement positive intrahepatic cholangiocarcinoma who received at least one dose of infigratinib, the centrally reviewed estimated ORR was 23.1% (95% confidence interval [CI]: 15.6%, 32.3%). The median duration of response (DOR) was 5.0 months; 8 of the 25 (32%) responders had a DOR lasting at least 6 months at the time of the analysis.

The review team considered that the ORR and DOR results in Study 2204 are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and represent a meaningful advantage over existing treatments for the proposed indication, and this satisfy the requirements for accelerated approval. FDA requested and QED has agreed to a postmarketing requirement to conduct a randomized clinical trial demonstrating improvement of progression-free survival or overall survival in patients with unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 gene fusion or rearrangement, to confirm the clinical benefit of infigratinib.

Concurrently with the approval of Truseltiq, FDA will approve the Foundation Medicine companion diagnostic assay (Foundation Medicine CDx) supplemental Premarket Approval (sPMA) application to select patients with cholangiocarcinoma harboring an FGFR2 gene fusion or other select rearrangement, for treatment with Truseltiq.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Cholangiocarcinoma (CCA) is a rare cancer arising from epithelial cells of bile ducts and is the second most common primary liver tumor worldwide after hepatocellular carcinoma (Blechacz 2017). In the US, it is estimated that there are approximately 8,000 to 10,000 new patients a year (American Cancer Society 2019). FGFR2 fusions have been detected in approximately 13% to 17% of intrahepatic CCA (Graham 2014; Ross 2014; Farshidfar 2017), and these fusions generally lead to ligand-independent constitutive activation of the receptor and downstream MAPK-ERK and JAK-STAT signaling pathways (Touat 2015; Babina 2017). Infigratinib (previously called BGJ398 and BBP-831) is a small molecule kinase inhibitor that is an ATP-competitive inhibitor of the fibroblast growth receptors (FGFRs) 1, 2, and 3.

There is no curative treatment for patients with advanced CCA. The standard of care for unresectable or metastatic disease is chemotherapy with cisplatin in combination with gemcitabine based on the results of the ABC-02 study (Del Valle 2010) and median survival is less than a year. For patients with FGFR2 fusions or other rearrangements who have progressed on at least 1 prior therapy, FDA granted accelerated approval to pemigatinib which is another FGFR inhibitor. There are no other FDA-approved drugs for the second-line treatment after disease progression on chemotherapy, irrespective of the presence of a biomarker.

The safety and effectiveness of infigratinib for the treatment of patients with advanced, unresectable CCA with FGFR2 fusions or other rearrangements and disease progression during or after systemic therapy was established by the results of Cohort 1 of an open-label, single-arm, international trial, CBGJ398X2204. Patients received infigratinib in 28-day cycles at a dosage of 125 mg orally once daily for 21 consecutive days, followed by 7 days off therapy. Infigratinib was administered until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

The median age was 53 years (range: 23 to 81 years), 62% were female, 72% were White, and all but one patient had a baseline Eastern Cooperative Oncology Group (ECOG) performance status score of less than 2 (ECOG 0: 42%; ECOG 1: 57%). Eighty-one percent of patients had FGFR2 gene fusions and 17% had FGFR rearrangements. Among the patients with in-frame FGFR2 gene fusions, the most common FGFR2 fusion identified was FGFR2-BICC1 (27%). Ninety-four percent of patients had metastatic

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

disease. All patients had received at least 1 prior line of systemic therapy, 32% and 29% had 2 or 3 prior lines of therapy, respectively.

The CBGJ398X2204 trial demonstrated a clinically meaningful and durable overall response rate (ORR) in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement, a serious and life-threatening disease. In the 108 patients with FGFR2 gene fusion/rearrangement-positive cholangiocarcinoma who received at least one dose of infigratinib, the estimated overall response rate (ORR) was 23.1% (95% confidence interval [CI]: 16%, 32%). At the time of the analysis, the median duration of response (DOR) was 5.03 months (95% CI: 3.71, 9.26); 8 of the 25 responders (32%) maintained the response for at least 6 months.

The CBGJ398X2204 trial also provided the primary data to support the safety of infigratinib for the proposed indication. An additional 243 patients with a variety of cancers treated with infigratinib as a single agent in 4 other multicenter single arm trials or cohorts of the CBGJ398X2204 trial provided additional, supportive safety data. Although assessment of a causal relationship between infigratinib and treatment-emergent reactions was limited given the single arm design of the trials providing safety data, the adverse reactions observed in patients treated with infigratinib were largely expected given the mechanism of action and the toxicity profile observed in preclinical studies. Among the 108 patients with cholangiocarcinoma enrolled in CBGJ398X2204, the most common adverse reactions to infigratinib (occurring at an incidence rate $\geq 20\%$) are nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting. The most common laboratory abnormalities were increased creatinine, and calcium-phosphate analyte abnormalities.

The serious risks of infigratinib include ocular toxicity (particularly retinal pigment epithelial detachment [RPED]) and hyperphosphatemia. Given the lack of systematic optical coherence tomography (OCT) assessments in all patients, asymptomatic cases of RPED were undetected and therefore the incidence rate is likely an underestimate of this risk. Likewise, the incidence of hyperphosphatemia is confounded by the use of prophylactic phosphate binders in 48% of patients (i.e., in the absence of hyperphosphatemia). Among the 351 patients who received infigratinib across clinical trials, RPED occurred in 11% of patients. The median time to first onset of RPED was 26 days. RPED led to dose interruption/reduction of infigratinib in 3.4% of patients and permanent discontinuation in 0.6% of patients. In order to mitigate the risk of severe RPED, comprehensive ophthalmologic monitoring including ocular coherence tomography is recommended prior to initiation of infigratinib, at 1 month, at 3 months and

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

every 3 months thereafter during treatment.

Among 108 patients who received infigratinib in CBGJ398X2204, hyperphosphatemia was reported in 89% of patients based on laboratory values above the upper limit of normal. Among 351 patients who received infigratinib across clinical trials, hyperphosphatemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-349). Phosphate binders were received by 83% of patients who received infigratinib. The median time to onset of hyperphosphatemia was 8 days (range 1-169).

Overall, the toxicity profile of infigratinib is considered acceptable when considering the anti-tumor effects (i.e., durable responses) in patients with previously treated cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement, who have a poor life expectancy and limited treatment options.. The risks of infigratinib are toxicities that oncologists are well-trained to manage, are largely reversible with dosage modification and supportive care, and overall are acceptable for a population with a serious and life-threatening condition.

Taken together, the review team concluded that the ORR and DOR results in CBGJ398X2204 provide evidence of infigratinib's effectiveness and recommends accelerated approval as the conditions of 21 CFR Subpart H have been met. Concurrently with the approval of infigratinib, FDA will approve the supplemental Premarket Approval (sPMA) application for the Foundation Medicine companion diagnostic assay (Foundation Medicine CDx), for the selection of patients with FGFR2 fusions or other select rearrangements for treatment with Truseltiq. FDA requested and QED has agreed to a postmarketing requirement (PMR) to conduct a randomized clinical trial demonstrating improvement of progression-free survival or overall survival in patients with unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 gene fusion or rearrangement, to confirm the clinical benefit of infigratinib. FDA requested additional PMRs related to further dose optimization and to study infigratinib in the pediatric population.

Dimension	• Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Cholangiocarcinoma (CCA) is a rare cancer arising from epithelial cells of bile ducts. CCA is grouped based on location of origin in the biliary tract: intrahepatic (iCCA), perihilar, or	Cholangiocarcinoma is a serious and life threatening disease.

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	• Evidence and Uncertainties	Conclusions and Reasons
	extrahepatic. Extrahepatic and perihilar cholangiocarcinoma are the most common types, with 6% to 8% of CCA being intrahepatic, 50% to 67% perihilar and 27% to 42% distal extrahepatic (DeOliveira 2007); CCA accounts for approximately 3% of all gastrointestinal cancers and 10-25% of primary hepatic malignancies worldwide and the incidence appears to be rising (Rizvi et al. 2013). Fibroblast growth factor/fibroblast growth factor receptor (FGFR) fusions have been identified as an early driver of oncogenic events in iCCA (Nakamura et al. 2015). FGFR2 fusions are present in an estimated 10-20% of patients with iCCA (Krook et al. 2020). Patients with FGFR rearrangements appear to have a longer median overall survival compared to those with iCCA lacking a FGFR rearrangement. In a retrospective review of 377 patients with CCA, patients with FGFR rearrangements had a median survival of 37 months compared to 20 months in the unselected CCA population (Jain et al. 2018). The baseline demographic and disease characteristics of patients with FGFR rearrangements also appear to be prognostically favorable, including diagnosis at a younger age and an earlier stage of disease. Patients with FGFR fusion-positive CCA are also predominantly female (63%) and usually have iCCA (87%).	

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Although surgery is the preferred treatment option for CCA, most patients have advanced-stage disease at the time of diagnosis, and only 35% are eligible for surgical resection with curative intent. For patients with advanced-stage or unresectable CCA, the median overall survival with standard of care chemotherapy is less than one year (Valle et al 2010).	
Current Treatment Options	Treatment options are limited, and no treatment has received regular FDA approval for treatment of patients with relapsed CCA. In the randomized study ABC-06 exploring chemotherapy with fluorouracil/leucovorin in combination with oxaliplatin (FOLFOX) vs. standard of care for the second line treatment of patients with CCA, patients receiving FOLFOX had a median OS benefit of 6.2 months compared to 5.3 months with best supportive care (hazard ratio [HR] 0.69; 95% CI: 0.50-0.97; p = 0.031) (Lamarca et al. 2019). This OS difference is modest, accompanied by a 5% ORR and significant toxicities associated with multiagent chemotherapy. Other regimens include irinotecan in combination with a fluoropyrimidine, a platinum plus fluoropyrimidine, gemcitabine in combination with a platinum or fluoropyrimidine, or regorafenib (NCCN 2020). Entrectinib and larotrectinib are approved for the treatment of patients with solid tumors that harbor NTRK gene fusions and who have no satisfactory alternative treatment options; however, NTRK gene fusions occur rarely in patients with CCA	Patients with CCA with a FGFR2 gene fusion or other rearrangement who have received at least one prior line of treatment have an unmet medical need. Current treatment options for patients with CCA are limited; pemigatinib, an FGFR inhibitor, was approved under the accelerated approval pathway and therefore is not considered available therapy. No drugs or biologics hold regular FDA approval for the treatment of patients with CCA in the second-line setting, irrespective of whether the tumor harbors an FGFR2 gene fusion or rearrangement.

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	• Evidence and Uncertainties	Conclusions and Reasons
	(i.e., in 1.3%)(Kheder et al 2018). Pembrolizumab is approved for the treatment of patients with microsatellite-high/mismatch repair deficient (MSI-high/dMMR) or tumor mutation-high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory treatment options; however, only approximately 4% of CCA are MSI-H/dMMR (Goeppert et al. 2019). Pemigatinib is approved under the accelerated approval regulations for the second line treatment of patients with CCA that harbors an FGFR2 gene alteration. The approval was based on the demonstration of a clinically meaningful and durable overall response rate (ORR) in 107 patients. The ORR in the FIGHT-202 study was 36% (95% 27%, 45%), with a median duration of response of 9.1 months and 63% of responders had a DOR lasting at least 6 months. As the approval was granted under 21 CFR 314, pemigatinib is not considered available therapy for regulatory decision making.	
Benefit	Study CBGJ398X2204 (also referred to as Study 2204, NCT02150967) provides the primary evidence demonstrating the effectiveness for infigratinib for the proposed indication. Study 2204 is an open label, non-randomized, multicohort trial; Cohort 1 evaluated infigratinib in 108 patients with locally advanced unresectable or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement,	The magnitude of effect on ORR observed in Study 2204 in patients treated with infigratinib is higher than that observed with FOLFOX (5% in Study ABC-06, Lamarca et al 2019) or other chemotherapy agents or combinations (current standard of care for CCA). The

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	whose disease had progressed on or after at least 1 prior systemic therapy (54% patients received at least 3 prior lines of therapy). Patients received infigratinib in 28-day cycles at a dosage of 125 mg administered orally once daily for 21 consecutive days, followed by 7 days off therapy until disease progression or unacceptable toxicity. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as determined by an independent review committee (IRC) according to RECIST v1.1. Study 2204 demonstrated a clinically meaningful and durable ORR in 108 patients with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 gene fusion or other rearrangement who received second line treatment with infigratinib. The estimated ORR was 23.1% (95% confidence interval [CI]: 15.6, 32.2) with a median duration of response (DOR) of 5.03 months (range: 0.92+, 19.12 months) by blinded independent central review (BICR). Of the 25 patients who achieved a confirmed complete response (CR) or confirmed partial response (PR) by BICR, 8 patients (32%) had a response duration ≥6 months.	duration of responses observed in patients with cholangiocarcinoma with a FGFR2 gene fusion who received prior treatment was clinically meaningful in the context of a disease with estimated survival of 5-6 months. The submitted evidence meets the statutory evidentiary standard for accelerated approval. QED has agreed to a postmarketing requirement to submit data from a randomized trial to verify and confirm the clinical benefit of infigratinib in patients with FGFR2 fusion/rearrangement- positive cholangiocarcinoma.

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The primary data supporting the safety of infigratinib for the proposed indication was provided from data derived from 108 patients with previously treated, locally advanced or metastatic cholangiocarcinoma who received at least one dose of infigratinib in Cohort 1 of CBGJ398X2204. The safety evaluation of infigratinib was also supported by data from an additional 243 patients with a variety of cancers treated with infigratinib 125 mg daily for 21-days of each 28-day cycle in clinical studies CBGJ398X2101, CBGJ398X2201, CBGJ398X2204 (Cohorts 1-3), and CBGJ398XUS04. In FDA's analysis, the recommended dosage of infigratinib has not been adequately justified. The dosage was selected on the MTD of the first-in-human study and has not been optimized. Exploratory analyses suggest a negative exposure-response and a positive exposure-toxicity relationship; 69% patients had some dosing modification for the management of toxicity. In addition, characterization of the effects of infigratinib in patients with renal and hepatic impairment was insufficient. Although assessment of a causal relationship between infigratinib and adverse reactions was limited in the context of the single arm design of the trials providing safety data, the toxicity profile was consistent with the mechanism of action and the toxicity profile observed in preclinical studies and other drugs targeting the same pathway. The important identified risks related to infigratinib are ocular toxicity (including retinal	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. Most of the adverse reactions to infigratinib were manageable with supportive care and dose modification as needed. The significant and potentially serious adverse reactions of hyperphosphatemia and ocular toxicity are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling. Although there were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS), the review team identified issues with infigratinib dose optimization and potential drug-drug interactions, which are being addressed in labeling and for which post-marketing requirements and commitments have been negotiated to further inform

NDA214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Dimension	• Evidence and Uncertainties	Conclusions and Reasons
	detachment, dry eye, and vision blurred) and hyperphosphatemia. Among the 108 patients with cholangiocarcinoma enrolled in CBGJ398X2204, the most common adverse reactions and lab abnormalities to infigratinib (incidence ≥ 20%) nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting. The most common laboratory abnormalities were increased creatinine, and calcium-phosphate analyte abnormalities.	labeling.

1.4. Patient Experience Data

No patient experience data was collected.

X

Sandra J. Casak, M.D.
Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Cholangiocarcinoma (bile duct cancer) is a rare, heterogeneous malignancy that originates from the neoplastic transformation of cholangiocytes into intrahepatic, perihilar, or distal extrahepatic tumors (Alpini 2002). Cholangiocarcinoma is the second most common primary liver tumor worldwide after hepatocellular carcinoma (Blechacz 2017; Khan 2012), affecting approximately 8,000 to 10,000 individuals a year in the United States (American Cancer Society 2019; Dana-Farber 2020). In the United States and other regions, the incidence of intrahepatic cholangiocarcinoma, specifically, has shown a marked increase in the last few decades (Bridgewater 2014; Saha 2016).

No predisposing factors are identified in most patients with cholangiocarcinoma, although there is evidence that the presence of chronic inflammation, such as primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, and liver fluke infections, might be associated with the disease in some patients (NCCN v1 2020). Other risk factors for intrahepatic cholangiocarcinoma have been found to include infections with hepatitis C virus and/or hepatitis B virus, obesity, cirrhosis, diabetes, alcohol, nonalcoholic fatty liver disease, and tobacco use (Welzel 2007).

The clinical presentation of cholangiocarcinoma patients is varied. Patients with intrahepatic masses may present with abdominal pain, malaise, night sweats, weight loss, and loss of appetite. Patients with extrahepatic cholangiocarcinoma tend to present with symptoms of obstructive jaundice and sometimes with complications like cholangitis (Ghouri 2015). There is no effective screening for cholangiocarcinoma; hence, most patients with cholangiocarcinoma are diagnosed at an advanced stage.

The growing understanding of the genetic alterations involved in the tumorigenesis of cholangiocarcinoma provides new therapeutic options for molecular targets. Among other genetic alterations, recurrent gene fusions involving the fibroblast growth factor receptor (FGFRs) are an important class of driver mutations in a number of tumor types, including cholangiocarcinoma (Wu 2013; Nakamura 2015). Kinase domain intact FGFRs can form fusions with various fusion partners and exhibit constitutive activation of the kinase activity, suggesting that these may serve as potential therapeutic targets via kinase inhibition. Cancer types harboring FGFR fusions are quite diverse. In addition to cholangiocarcinoma (Arai 2014; Sia 2015; Churi 2014; Graham 2014), FGFR2 fusions with different partners have been detected in bladder, thyroid, prostate, pancreatic, breast, lung, glioma, and other cancer types (Parker

2014; Wu 2013; Helsten 2016; Babina 2017).

FGFR2 fusions are the most common FGFR genetic aberrations in cholangiocarcinoma (Jain 2016). FGFR2 fusions with different partners, such as BICC1, TACC3, CCDC6, and AHCYL1, have been detected in approximately 13% to 17% of intrahepatic cholangiocarcinomas (Graham 2014; Ross 2014; Farshidfar 2017). FGFR fusion partners generally contain dimerization or oligomerization domains that lead to ligand-independent constitutive activation of the receptor and downstream MAPK-ERK and JAK-STAT signaling pathways (Touat 2015; Babina 2017), resulting in uncontrolled cell proliferation, survival and migration, which are hallmarks of cancer. FGFR inhibition reduces cancer cell proliferation in vitro, decreases tumor growth in in vivo FGFR2 fusion-positive cholangiocarcinoma models, and has demonstrated single-agent responses in patients with cholangiocarcinoma harboring FGFR2 fusions. Resistance can develop through mutations in FGFR2, further supporting FGFR2 fusions as a therapeutic target for molecularly selected patients with cholangiocarcinoma (Lamarca 2020; Goyal 2017).

Only a few studies have assessed the natural history of cholangiocarcinoma with FGFR2 genetic alterations. These are limited by being retrospective studies that included patients who have received targeted treatments such as FGFR inhibitors; and the few studies evaluating previously treated patients are additionally limited by small sample sizes. In general, these studies have not yielded clear results as to whether FGFR2 alterations are prognostically favorable. To further evaluate the natural history, QED has conducted retrospective analyses of the natural history of cholangiocarcinoma by investigating the overall survival (OS) of patients with cholangiocarcinoma and FGFR2 fusions/rearrangements and those with FGFR2 WT cholangiocarcinoma using real-world data from Flatiron Health and Foundation Medicine and assessing response and progression-free survival for patients within the registrational study who received second-line chemotherapy, in addition to review of the literature. Similar to the retrospective studies, the real-world data included patients who received investigational agents (nonspecified) and kinase inhibitors with FGFR inhibitory activity; thus, receipt of FGFR inhibitors may have positively impacted survival for the FGFR fusion-positive group. Taken together, existing data on the natural history of FGFR2 fusion-positive cholangiocarcinoma does not appear to show a clear survival advantage for FGFR2 fusion-positive patients over WT cholangiocarcinoma patients receiving standard therapy and no progression-free survival (PFS) advantage has been demonstrated for first- or second-line treatment with chemotherapy for the two populations. Data that are available for patients with FGFR2 fusion-positive cholangiocarcinoma in the second-line setting indicate mPFS of 4-5 months, with no responses; similar to mPFS of 3.2-4 months and response rates of 5%-7% reported in unselected patients (summarized in the Clinical Overview, Appendix 7.1).

Given the seriousness of the disease, the poor survival, and the few treatment options, infigratinib represents a potential new targeted treatment option that has been demonstrated to have antitumor activity and provide durable, meaningful clinical benefit to patients with

previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.

The FDA's Assessment:

FDA agrees that cholangiocarcinoma (CCA) is a serious and life-threatening disease. Approximately 8,000 new cases of CCA are diagnosed each year in the U.S. (American Cancer Society) and advanced/metastatic CCA has a 5-year survival rate less than 10% (Fostea 2020). In a retrospective analysis of the SEER database of CCA cases in the US during 2000-2015, of 16,189 patients with cholangiocarcinoma, 64.4% were intrahepatic. Most patients were White (78.4%), males (51.3%), and older than 65 years (63%). CCA incidence and mortality were 11.977 and 10.295 and were both higher among Asians, males, and individuals older than 65 years (Gadab M, 2020). CCAs can be further classified into intrahepatic or extrahepatic tumors based on their location with respect to the hilum. Genetic aberrations found in intrahepatic CCAs include isocitrate dehydrogenase 1 and 2 (IDH 1/2) mutations and fibroblast growth factor receptor (FGFR) fusions; KRAS Proto-Oncogene (KRAS), Tumor Protein P53 (p53), and SMAD Family Member 4 (SMAD4) mutations are more commonly observed in extrahepatic tumors (Jain 2016). FDA acknowledges QED's interpretation of the literature and RWE data but notes that the prognostic value of FGFR rearrangements is somewhat controversial; in a retrospective review of 377 patients with CCA, the reported median OS was 37 months in patients with FGFR gene fusion positive CCA compared to 20 months in the unselected CCA population (Jain et al. 2018). In this retrospective analysis, the baseline demographic and disease characteristics of patients with FGFR rearrangements also appear to be prognostically favorable, including diagnosis at a younger age and an earlier stage of disease. Patients with FGFR fusion-positive CCA are also predominantly female (63%) and the location is intrahepatic for the majority of patients (87%). Furthermore, QED describes in the submission that in the retrospective analysis of the natural history of cholangiocarcinoma conducted using real-world data from Flatiron Health and Foundation Medicine, a preliminary assessment of these real-world data yielded similar results to the retrospective studies, with a non-statistically significant trend toward longer survival in patients with cholangiocarcinoma and FGFR2 fusion or rearrangement compared with patients with wild-type tumors. An analysis of OS for patients with FGFR2 fusion/rearrangement cholangiocarcinoma following second-line chemotherapy (n = 50) demonstrated a median OS of 8.45 months (95% CI: 4.15, 12.43), although some of these patients may have received investigational agents (non-specified) and kinase inhibitors with FGFR inhibitory activity, which may have positively impacted survival for the FGFR fusion-positive group.

2.2. Analysis of Current Treatment Options

For advanced cholangiocarcinoma patients who relapse after first-line therapy, a meta-analysis of available treatments supported a mean OS of 7.2 months with a mean progression-free survival (PFS) of 3.2 months and mean response rate of 7.7% ([Lamarca 2014](#)). The only standard of care second-line option supported by randomized data is fluorouracil/leucovorin in combination with oxaliplatin (mFOLFOX) + active symptom control in Study ABC-06, with a response rate of 5%, median PFS of 4 months, and median OS of 6.2 months ([Lamarca 2019](#)). In the ABC-06 trial, the most frequent Grade 3/4 adverse events (AEs) reported in the mFOLFOX group included fatigue/lethargy (19%), biliary event (19%), infection (14%), and neutrophil count decreased (12%) ([Lamarca 2019](#)). For patients who elect to receive best supportive care instead of cytotoxic chemotherapy, the ABC-06 trial indicates that outcomes are even poorer, with a median OS of 5.3 months. Other available regimens include FOLFIRI and regorafenib, both based upon category 2B evidence ([NCCN v5 2020](#)). The recent FDA accelerated approval of pemigatinib for patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement substantiates the importance of FGFR2 fusions or rearrangements as a promising target for therapy in advanced cholangiocarcinoma. Despite these advances, an urgent need remains for additional, less toxic, effective therapies.

Entrectinib and larotrectinib are approved for solid tumors that have NTRK gene fusions, and pembrolizumab for the treatment of patients with solid tumors that are microsatellite-high/mismatch repair deficient (MSI-high/dMMR). However, these are rare genetic aberrations in cholangiocarcinoma with MSI-H/dMMR and NTRK fusions in approximately 1.3% and 4%, respectively ([Goepfert 2019](#); [Kheder 2018](#)). Additional available treatments in certain circumstances include ivosidenib for cholangiocarcinoma with *IDH1* mutations ([NCCN v5 2020](#)); however, *IDH1* mutations and FGFR2 fusions seem to be mutually exclusive ([Farshidfar 2017](#); [Di Stefano 2015](#)).

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 1: Summary of Currently Available Treatments for Patients with Previously Treated Cholangiocarcinoma with FGFR2 fusion

Product (s) Name	Relevant Indication	Year And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FGFR inhibitors					
Pemigatinib (Pemazyre®)	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.	2020 Accelerated Approval	13.5 mg/day for 14 days followed by 7 days off (21-day cycles)	ORR: 36% (95% CI: 27, 45); CR: 2.8%, PR: 33% Median DOR: 9.1 months (95% CI: 6.0, 14.5) Patients with DOR ≥ 6 months: 24 (63%) DOR ≥ 12 months: 7 (18%)	- Ocular Toxicity - Hyperphosphatemia - Embryo-fetal Toxicity
Available Treatments for patients with Cholangiocarcinoma regardless of presence of FGFR2 Fusion or Rearrangement					
mFOLFOX NCCN Guidelines V3, 2020. Recommendation Category 2A	No relevant indications for cholangiocarcinoma	N/A	No labeled dosing in this setting. However, in the ABC-06 trial, the regimen was administered as follows: Oxaliplatin 85mg/m ² , L-folinic acid 175mg (or folinic acid 350mg), 5 FU 400mg/m ² (bolus), 5FU 2400mg/m ² 46 hours continuous infusion every 14 days for up to 12 cycles	In the Phase 2 randomized ABC-06 study (Lamarca 2019), in patients with advanced biliary tract cancer after disease progression to cisplatin + gemcitabine: Median OS: 6.2 months, adjusted HR 0.69 (95% CI 0.50 – 0.97; p=0.031) ORR: 5% (CR 1%, PR 4%)	- Neutropenia - Infections - Peripheral Neuropathy

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Product (s) Name	Relevant Indication	Year And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FOLFIRI (NCCN Guidelines V3, 2020. Recommendation Category 2B)	No relevant indications for cholangiocarcinoma	N/A	No labeled dosing in this setting. However, in the study supporting the Category 2B recommendation (Caparica 2019), FOLFIRI was administered per this institution's standard practice (fluorouracil 400mg/m ² bolus on D1 then 2400 mg/m ² on a 48h protracted infusion D1-2, leucovorin 200 mg/m ² on D1 and irinotecan 180 mg/m ² on D1 every 14 days, with each administration being considered 1 cycle)	In a retrospective cohort study in patients with locally advanced or metastatic biliary tract cancer who progressed after at least one line of chemotherapy (Caparica 2019): Median PFS: 1.7 months (95% CI: 0.66 – 2.57) Median OS: 5 months (95% CI: 2.77 – 7.2)	• Myelosuppression • Diarrhea • Renal impairment/renal failure • Embryo fetal toxicity
Larotrectinib (Vitrakvi®)	For the treatment of adults with solid tumor who have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation (tumor agnostic)	2018 Accelerated Approval	100 mg orally twice daily capsule	ORR: 75% (95% CI: 61, 85); CR: 22%, PR: 53% DOR range (months): 1.6+, 33.2+ DOR ≥ 6 months: 73% DOR ≥ 12 months: 39%	• Neurotoxicity • Hepatotoxicity • Embryo-fetal toxicity

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

Product (s) Name	Relevant Indication	Year And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Entrectinib (Rozlytrek®)	For the treatment of adults with solid tumor who have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation (tumor agnostic)	2019 Accelerated Approval	600 mg orally once daily capsule	ORR: 57% (95% CI: 43, 71); CR: 7.4%, PR: 50% DOR range (months): 2.8, 26+ DOR ≥ 6 months: 68% DOR ≥ 12 months: 45%	• Congestive heart failure • Central nervous system effects • Skeletal fractures • Hepatotoxicity • Hyperuricemia • QT Interval Prolongation • Vision Disorders • Embryo-fetal toxicity
Pembrolizumab (Keytruda®)	For the treatment of adults with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options (tumor agnostic)	2014 Approval	200 mg IV every 3 weeks	In patients with MSI-H or mismatch repair deficient cholangiocarcinoma who experienced failure with prior therapy (Marabelle 2019) ORR: 40.9% (20.7-63.6) mPFS: 4.2 months mOS: 24.3 months	• Immune-Mediated Pneumonitis • Immune-Mediated Colitis • Immune-Mediated Hepatitis • Immune-Mediated Endocrinopathies • Immune-Mediated Nephritis and Renal Dysfunction • Immune-Mediated Skin Adverse Reactions • Other Immune-Mediated Adverse Reactions • Infusion-Related Reactions • Embryo-fetal toxicity

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Product (s) Name	Relevant Indication	Year And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Ivosidenib (Tibsovo®) NCCN Guidelines V3, 2020. Recommendation Category 2A	No relevant indications for cholangiocarcinoma	N/A	No labeled dosing guidelines in this setting. However, in the ClarIDHy study the following dose was used: 500 mg orally once daily (28-day cycles) (Abou-Alfa 2020)	In the Phase 3 ClarIDHy study in patients with advanced, IDH1-mutant cholangiocarcinoma who had progressed on previous therapy (Abou-Alfa 2020): Median PFS: 2.7 months (95% CI 1.6 – 4.2); hazard ratio: 0.37 (95% CI 0.25 - 0.54); p <0.0001	• Differentiation Syndrome • QTc Interval Prolongation • Guillain-Barré Syndrome
Regorafenib (Stivarga®) NCCN Guidelines V3, 2020. Recommendation Category 2A	No relevant indications for cholangiocarcinoma	N/A	No labeled dosing guidelines in this setting. In the Phase 2 study (Sun 2019), the following dose was used: 120 mg once daily for 21 days followed by 7 days off (28-day cycle)	In the single arm-Phase 2 study in patients with advanced/unresectable or metastatic biliary tract cancer who failed at least 1 line of systemic chemotherapy (Sun et al., 2019): Median PFS: 15.6 weeks (90% CI 12.9 – 24.7 weeks) Median OS: 31.8 weeks (90% CI: 13.3 – 74.3 weeks)	• Hepatotoxicity • Hemorrhage • Dermatological toxicity • Hypertension • Cardiac ischemia and infarction • Reversible posterior leukoencephalopathy syndrome • Gastrointestinal perforation or fistula • Wound healing complications • Embryo-fetal toxicity

*Accelerated approval or full approval

The Applicant's Position:

Cholangiocarcinoma is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis. The only chance for cure is surgical resection, for which only approximately one-third of patients are eligible (Lamarca 2014). Standard of care first-line treatment of advanced or metastatic cholangiocarcinoma has a median survival of <1 year (Valle 2010). Further supporting the lack of therapeutic options, the 5-year survival rate for patients with cholangiocarcinoma was reported to be less than 10% (Everhart 2009). For patients who have progressed after first-line treatment, there are few therapeutic options and there remains a significant unmet need for new therapies, including targeted agents such as infigratinib.

The clinically relevant magnitude and duration of benefit observed support the use of infigratinib to treat this serious and life-threatening disease in a refractory patient population (previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other rearrangements) who has few effective therapeutic options and no established standard of care.

Infigratinib has a predictable and manageable safety profile that is considered acceptable when considering the antitumor effects (i.e., clinically relevant magnitude and duration of benefit) in patients with cholangiocarcinoma harboring an FGFR2 fusion or other rearrangement, who have a poor life expectancy and limited treatment options. The major safety risks of infigratinib are toxicities that oncologists are well-trained to manage and are acceptable for a population with a serious and life-threatening condition. Finally, infigratinib could provide an oral, chemotherapy-free treatment option for treatment of advanced cholangiocarcinoma, decreasing the risk of immunosuppression and the additional patient burden associated with chemotherapy infusions, which both patients and physicians desire.

Overall, the data support that infigratinib has the potential to offer a considerable improvement, from both a nonimmunosuppressive safety profile and efficacy perspective, over established chemotherapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's analysis of current treatment options for previously treated CCA that is presented above. The combination of gemcitabine and cisplatin is standard first-line therapy for advanced/metastatic CCA (Valle 2010). Second-line treatment options include FOLFOX, FOLFIRI, single-agent gemcitabine, and clinical trial regimens (Lamarca 2019; Lowery 2019). However, none of these therapies have been approved for the second line treatment and none has demonstrated a survival advantage with the exception of FOLFOX which demonstrated a median OS of 6.2 months compared to 5.3 months for active symptom control in the ABC-06 trial (HR was 0.69 [95% CI 0.50-0.97]; $p = 0.031$). In the context of a very modest effect on survival and with the toxicities associated with the administration of FOLFOX,

this treatment may not be considered as the standard of care for many patients (Lamarca 2019).

As shown in Table 1, FDA granted accelerated approval of pemigatinib in April 2020 for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement as detected by an FDA-approved test. Pemigatinib is an oral small molecule kinase inhibitor that inhibits the kinase activities of FGFR1, 2, and 3. Accelerated approval was granted based on the FIGHT-202 trial which was an open label, non-randomized, multi-cohort study in patients with locally advanced unresectable or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement, whose disease had progressed on or after at least one prior therapy. In the first 107 patients with FGFR2 gene fusion/rearrangement--positive cholangiocarcinomas who received at least one dose of pemigatinib, the estimated overall response rate (ORR) was 36% (95% confidence interval [CI]: 27%, 45%). The most common adverse events of pemigatinib were hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, and dry eye. Concurrently with the approval of pemigatinib, FDA approved the supplemental Premarket Approval (sPMA) application for the Foundation Medicine companion diagnostic assay (Foundation Medicine CDx), for the selection of patients with FGFR2 fusions or other rearrangements for treatment with pemigatinib.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Infigratinib is not currently approved in the United States or any other country.

The FDA's Assessment:

FDA agrees.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

IND 104,187 was originally submitted on 04 September 2009 by the previous sponsor and transferred to QED on 19 September 2018. A summary of QED's key interactions with the FDA regarding infigratinib development and Study CBGJ398X2204 (a phase 2, single arm study of infigratinib in patients with advanced cholangiocarcinoma), the pivotal study for this NDA, is provided in [Table 2](#) below.

Table 2: Key FDA Interactions for IND 104,187

Type of Meeting	Date	Event Summary
Type C Meeting	10 DEC 2018	Discussion of nonclinical and clinical pharmacology plans, registration of infigratinib for second-line cholangiocarcinoma.
Type C Meeting	17 APR 2019	Discussion of CMC development program for infigratinib and registration plans for the first indication of infigratinib.
Type C Meeting	07 AUG 2019	Discussion of structure, format and proposed integrated safety analyses for the proposed NDA.
NA	11 SEP 2019	Orphan Drug Designation granted for cholangiocarcinoma.
Type C Meeting	20 DEC 2019	Discussion of (1) pooling safety and efficacy data across formulations, (2) the proposed primary efficacy analysis to support an NDA based on results from Cohort 1 of Study CBGJ398X2204 (3) narratives to be included in the NDA, and (4) assessments of important safety outcomes.
Type C Meeting	08 APR 2020	Discussion of proposed drug product release and stability specifications, the testing conducted to explore the discriminating ability of the QC dissolution method, and the stability data requirements.
Type F Meeting	02 JUN 2020	Discussion of amended initial Pediatric Study Plan.
Type B Meeting	28 JUL 2020	Discussion of adequacy of topline data from Study CBGJ398X2204 and contents of a complete NDA.

The FDA's Assessment:

FDA agrees with the Applicant's summary of pre submission/submission key regulatory milestones presented above. Additional pertinent regulatory history that is not described above is summarized below:

- On September 10, 2019 Fast Track Designation was granted for the first-line treatment of adult patients with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations.
- On October 24, 2020, FDA issued an "Amended Agreed Initial Pediatric Study Plan-Agreement" letter to QED for Cholangiocarcinoma with fibroblast growth factor receptor (FGFR)2 fusions.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of the study sponsor (QED.) and the clinical sites with the highest (site #5003) and second-highest (site #5001) patient enrollment. None of these three sites had been inspected by FDA prior to this NDA. OSI conducted on-site surveillance inspections of these three sites between December 2020 and January 2021. Overall, OSI concluded the following:

- The protocol-required ophthalmic safety assessments performed at site #5001 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. 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, it is unlikely that any of the violations had a significant impact on subject safety or data integrity.

The Office of Scientific Investigations concluded that the clinical data generated from the three inspected sites and submitted to the NDA by QED appear to be reliable and supportive of this NDA and the proposed indication for infigratinib.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of infigratinib capsules under this NDA. Refer to the OPQ review of this application for additional information. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC).

Pursuant to 21 CFR 25.31(b), QED submitted a Request for Categorical Exclusion from the preparation of an environmental assessment for infigratinib and submitted environmental assessment data to support this request. OPQ determined that this request could be granted, as the estimated concentration of the drug substance at the point of entry into the aquatic environment (EIC) is projected to be (b) (4) parts per billion (ppb), less than the 1 ppb limit that allows an exclusion to be granted.

4.3. Clinical Microbiology

This NDA was reviewed by OPQ's Division of Microbiology Assessment. The microbiology reviewers did not identify any issues that would preclude approval of infigratinib tablets. Infigratinib should be stored at room temperature 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

4.4. Devices and Companion Diagnostic Issues

Foundation Medicine submitted a supplemental Premarket Approval (sPMA) application to the Center of Devices and Radiological Health (CDRH) for the Foundation OneCDx (F1 CDx) intended for the selection of patients with FGFR2 fusions or select rearrangements for treatment with infigratinib.

Tissue samples were originally screened using local and central tests for enrollment in the CBGJ398X2204 trial evaluating infigratinib; 108 patients with confirmed FGFR2 fusion/rearrangements by clinical trial assays (CTAs) were enrolled. 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. The sensitivity analysis of clinical efficacy for the F1CDx positive population ranged from 21.68% to 22.49% per the average among the 50 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 select the patient population that may have clinical benefit with infigratinib use. The device will receive marketing approval concurrent with approval of this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical development program included in vitro cellular assay systems and in vivo studies in the mouse, rat, rabbit, and dog to evaluate infigratinib pharmacology, pharmacokinetics, toxicology, genotoxicity, reproductive, and developmental effects. Infigratinib (also known as BGJ398, BBP-831, infigratinib phosphate) is a small molecule, ATP-competitive inhibitor of fibroblast growth factor receptor. The established pharmacological class for infigratinib is kinase inhibitor.

The FGFR family of receptor tyrosine kinases (RTKs) consists of high-affinity receptors for more than 20 FGF ligands. Aberrant FGFR signaling is activated in various human cancers with point mutations, amplifications, overexpression, and chromosomal translocations leading to uncontrolled proliferation.

Infigratinib had in vitro inhibitory activity against FGFR1, FGFR2, and FGFR3 with IC50 values in the low nanomolar range (1–2 nM) and against FGFR4 with IC50 value of 61 nM. Constitutive FGFR signaling can support the proliferation and survival of malignant cells. Infigratinib inhibited FGFR1, FGFR2, and FGFR3 phosphorylation, signaling, and decreased cell viability in cancer cell lines with activating FGFR amplifications, mutations, and fusions that result in constitutive activation of FGFR signaling. Infigratinib exhibited anti-tumor activity in mouse and rat xenograft models of human tumors with activating FGFR2 or FGFR3 alterations, including patient-derived xenograft models of cholangiocarcinoma with FGFR2-fusions.

Major human metabolites BHS697 and CQM157 bind FGFR1, FGFR2, and FGFR3 with similar affinity to infigratinib (BHS697 Kd 0.46–0.87 nM; CQM157 Kd 0.34–1 nM; infigratinib Kd 0.53–1.2 nM).

Safety pharmacology studies with infigratinib assessed the effects on cardiovascular, central nervous system (CNS), and respiratory function. Infigratinib had no toxicologically significant effects on cardiovascular function in telemetered dogs or on neurobehavioral and respiratory functions in rats.

The Applicant conducted 13-week repeat-dose toxicology studies in rats and dogs with a recovery period of 6 weeks. Infigratinib was dosed once daily by oral administration at 0 (vehicle control), 1, 3, or 10 mg/kg/day. At the high dose of 10 mg/kg/day, findings in rats included dose-dependent bone growth plate thickening in the femur and sternum and tooth degeneration. Ocular toxicities included microscopic corneal mineralization and keratopathy with clinical signs of corneal opacity in male rats; there was no reversibility for ocular

mineralization after the 6-week period in male rats at 10 mg/kg/day. Increased serum phosphate was observed, and mineralization occurred in several tissues including the kidney. Increases in AST, ALP, urea, and creatinine were observed. In the 13-week study in dogs, bone toxicities were observed at 1 and 3 mg/kg/day. Dogs also showed skin-related findings of acinar atrophy and hyperkeratosis and gastrointestinal (GI)-related findings including decreased mean body weight gains and food consumption at 10 mg/kg/day. Observations in dogs were reversible after the 6-week recovery period. The metabolite BQR917 was disproportionately higher than that of infigratinib in dog.

Toxicology studies in rat and dogs assessed the toxicity of infigratinib after once daily oral administration up to 26 weeks in rats and 39 weeks in dog (high dose of 3 mg/kg/day in both species). Oral dosing in animals was consistent with the intended clinical route of administration for infigratinib. Targets of toxicity included bone (decreases in bone strength, decreases in total bone mineral density, and multifocal growth plate fractures) and liver (centrilobular vacuolation and mild focal necrosis in the rat).

A fertility and embryo-fetal development study was conducted in rats with infigratinib administered orally once daily at doses of 0.3, 1, or 3 mg/kg/day. Dosing in male rats started 15 days before cohabitation and continued during cohabitation through the week before study termination (for a minimum of 35 doses). Dosing in females started 15 days before cohabitation and continued during cohabitation until gestation day (GD) 7. No effects were observed on mating or fertility in males or estrous cycling parameters in female rats. There was a decrease in the mean number of embryos post-implantation, with an increase in nonviable embryos at 3 mg/kg/day.

An embryo-fetal developmental toxicology study was conducted in rats with infigratinib administered orally once daily at doses of 1, 3, or 10 mg/kg/day. The high dose of 10 mg/kg/day resulted in increased embryofetal lethality with reductions in the number of viable fetuses and in fetal body weights at ≥ 3 mg/kg/day (<0.1 times the human exposure at the clinical dose of 125 mg). Fetal abnormalities included external, visceral, and skeletal malformations and variations were increased at ≥ 1 mg/kg/day (<0.1 times the human exposure at the clinical dose of 125 mg).

An additional embryo-fetal developmental toxicology study was conducted in rabbits with infigratinib administered orally once daily at doses of 0.3, 1, or 3 mg/kg/day from GD 7 to GD 19. Infigratinib administration resulted in maternal toxicity and a corresponding reduction in fetal body weight.

Based on the toxicity profile of infigratinib and the elimination half-lives of active metabolites (e.g., median ~ 53 hr for CQM197), FDA agrees with labeling in sections 8.2 and 8.3 regarding

avoidance of breastfeeding for one month following the final dose and using effective contraception for one month following the final dose.

Infigratinib was not mutagenic in the bacterial reverse mutation test. Infigratinib was not clastogenic in an in vitro human peripheral blood lymphocyte chromosome aberration assay or an in vivo bone marrow micronucleus assay in rats. Carcinogenicity studies are not warranted to support a marketing application for the proposed indication.

The submitted nonclinical pharmacology and toxicology data are adequate to support the indication of infigratinib for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement. This application is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

None.

5.3. Pharmacology

Primary pharmacology

Infigratinib is a small molecule, ATP-competitive inhibitor of fibroblast growth factor receptor.

Biochemical studies showed ATP-competitive inhibition of FGFR1 (IC₅₀ of 1.1 nM), FGFR2 (IC₅₀ of 1 nM), FGFR3 (IC₅₀ of 2 nM), and FGFR4 (IC₅₀ of 61 nM) (Study No. RD-2018-00444 using a 126-kinase panel platform).

Table 3: Infigratinib Inhibitory Activity Using a 126-Kinase-Platform Assay

Receptor	IC ₅₀ (nM)
FGFR1	1.1
FGFR2	1
FGFR3	2
FGFR4	61

In a HEK293 cell-based ELISA (Studies #RD-2005-01708, RD-2005-01709, RD-2005-01712, RD-2005-01668), infigratinib inhibited tyrosine phosphorylation of FGFR1, FGFR2, and two mutated, constitutively activated forms of FGFR3 commonly found in human tumor cells, FGFR3^{K650E} and FGFR3^{S249C}.

Table 4: Infigratinib Inhibitory Activity in a Cell-Based ELISA Assay

Receptor	IC ₅₀ (nM)
FGFR1	4.6
FGFR2	4.3
FGFR3 ^{K650E}	5.6
FGFR3 ^{S249C}	4.8
FGFR4	164

Kd values for infigratinib and its major human metabolites, BHS697 and CQM157, were determined using the KINOMEScan assay system, where the two metabolites had similar binding affinity.

Table 5: In Vitro Binding of Infigratinib and Metabolites BHS697 and CQM157 to FGFRs

	BHS697 Kd (nM) (2 Experiments)		CQM157 Kd (nM) (2 Experiments)		Infigratinib Kd (nM)
FGFR1	0.46	0.63	0.85	1	0.53
FGFR2	0.7	0.23	1	0.34	1.2
FGFR3	0.48	0.87	0.57	0.71	0.7
FGFR4	15	37	18	29	29

Excerpted from Applicant's Submission

Anti-proliferative activity of infigratinib was measured in human bladder cancer (RT112, RT4), endometrial cancer (AN3CA, MFE296, HEC-1B), multiple myeloma (KMS11, OPM2), and myeloproliferative syndrome 8p11 cell line KG1. Each of these cell lines has a specific FGFR alteration, including mutations. Downstream inhibition of the RAS-MAPK pathway resulted in diminished tyrosine phosphorylation and ERK/MAPK inactivation in cancer cell lines.

Table 6: Anti-proliferative Activity of Infigratinib in Human Cell Lines

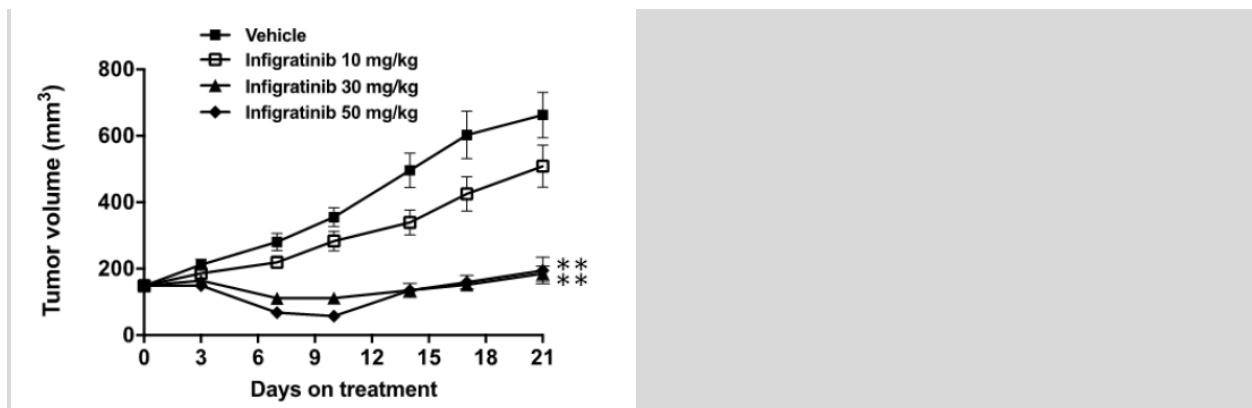
Cancer Type	Cell Line	FGFR Alteration	IC ₅₀ ± SD (nM)	N
Bladder cancer	RT112	FGFR3 fusion/amplification/ overexpression	4.4 ± 2.4	21
	RT4		21 ± 16	7
	MGHU3	FGFR3 activating mutation	25	2
	VMCUB1, J82	Low or undetectable FGFR3	>3000	3
Endometrial cancer	AN3CA	FGFR2 activating mutation	26 ± 9	6
	MFE296		248 ± 54	4
	HEC-1B	FGFR2 WT	>3000	2
Multiple myeloma	KMS11	t(4,14) translocation → FGFR3	10 ± 3	8
	OPM2	overexpression; FGFR3 mutations	55 ± 22	14
8p11 myeloproliferative syndrome	KG1	FGFR1OP2/FGFR1 fusion protein due to chromosomal translocation	1.7 ± 0.6	8

N=number of independent experiments conducted; SD=standard deviation, WT=wild type.

Excerpted from Applicant's Submission

In vivo inhibitory activity of infigratinib was assessed in a patient-derived xenograft (PDX) using BALB/c nude mice subcutaneously implanted with cholangiocarcinoma CC6702 tumor cells harboring an FGFR2-TTC28 fusion. Oral administration at 10, 30, or 50 mg/kg infigratinib once daily resulted in tumor growth inhibition (TGI) of ~30%, 93%, and 91%, respectively, by the end of the experiment on Day 21.

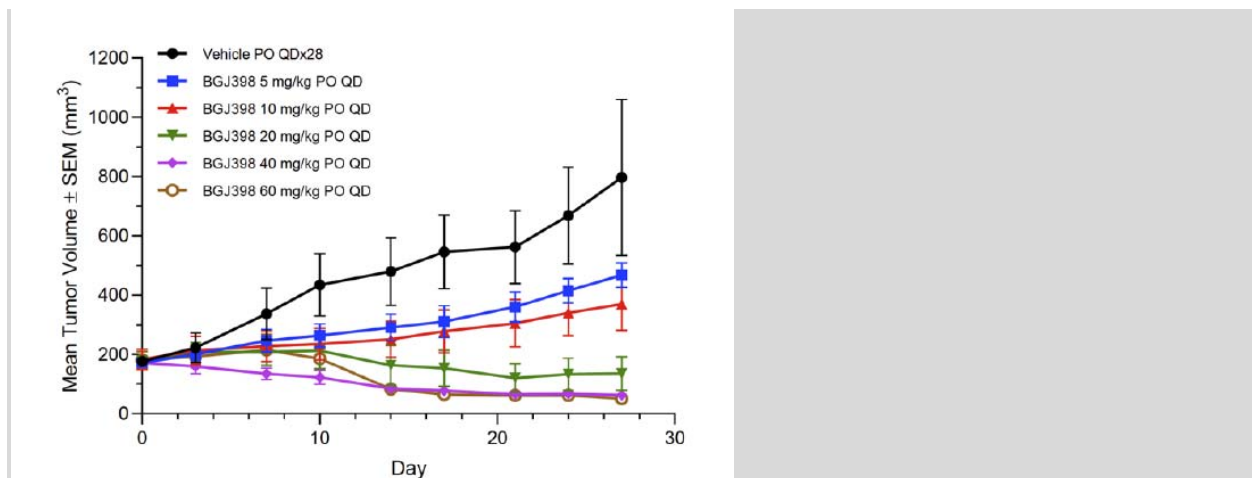
Figure 1: Infigratinib Antitumor Efficacy in a PDX Mice Model with Cholangiocarcinoma



Excerpted from Applicant's Submission

In a PDX model with the human cholangiocarcinoma line CTG-0997, harboring a FGFR2-TRA2B fusion, orally administered infigratinib at daily doses from 10 to 60 mg/kg/day had statistically significant antitumor activity compared to vehicle.

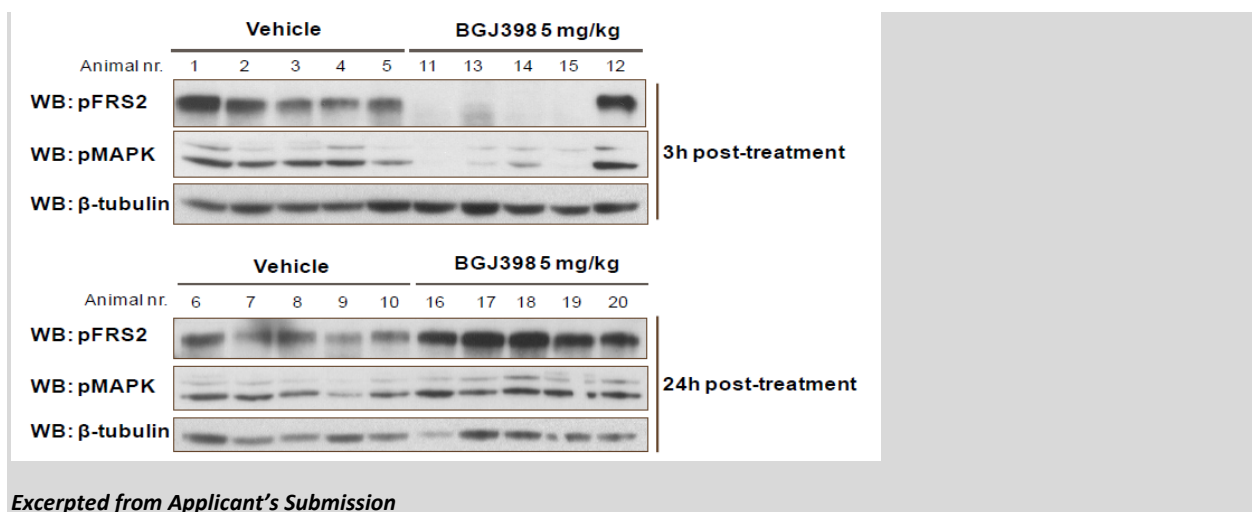
Figure 2: Infigratinib Antitumor Activity in CTG-0997 Cholangiocarcinoma PDX Mice



Excerpted from Applicant's Submission

In a urothelial cancer model using RT112 bladder cancer cells harboring an FGFR3-TACC3 fusion (Study RD-2008-00646), RT112 xenograft-bearing athymic rats were administered 5, 10, or 15 mg/kg oral infigratinib once daily for 14 days. Xenografted tissue from the vehicle and 5 mg/kg infigratinib groups was analyzed by western blot to evaluate the inhibition of the FGFR pathway and reduction in FRS2 tyrosine phosphorylation (pFRS2) and MAPK phosphorylation (pMAPK).

Figure 3: Western Blot Analysis of FRS2 Phosphorylation (pFRS2) and MAPK Activation in RT112 Tumor Xenografts



Secondary Pharmacology

The Applicant's Position:

Infigratinib is an orally bioavailable, potent, and selective ATP-competitive inhibitor of FGFR1-3. In vitro, infigratinib inhibited the activity of FGFR1-3, but not FGFR4, KDR and other kinases, at clinically relevant concentrations. Infigratinib inhibited FGFR2 (the primary target involved in efficacy of infigratinib in cholangiocarcinoma) with an IC_{50} of 1nM. In vivo, infigratinib significantly inhibits tumor growth in PDX models of human cholangiocarcinoma driven by distinct FGFR2 fusions. Infigratinib and its major metabolites BHS697 and CQM157 were shown to inhibit various targets in secondary pharmacology screens. However, based on the unbound concentrations of infigratinib and the metabolites at the recommended clinical dose of infigratinib (125 mg QD), it is unlikely that these targets would be affected.

The FDA's Assessment:

Based on the possible range for unbound C_{max} , inhibition of FGFR4 may be relevant.

Safety Pharmacology

The Applicant's Position:

In vivo safety pharmacology studies conducted in rats and dogs identified no potential for infigratinib to cause cardiovascular, neurofunctional, or respiratory effects. Infigratinib and the metabolites BHS697 and CQM157 inhibited hERG current but at concentrations that were much higher than peak exposure of each in humans at the recommended clinical dose of infigratinib (125 mg QD). Thus, it is unlikely infigratinib or its major metabolites would prolong the QTc interval at clinically meaningful exposures. This conclusion is in accordance with the lack of ECG changes noted in the single and repeat-dose dog cardiovascular safety pharmacology studies and in repeat-dose dog toxicity studies where these metabolites were present at close to or above clinically relevant concentrations.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Infigratinib was evaluated in an in vitro hERG patch-clamp assay with human embryonic kidney cells. Infigratinib hERG inhibition at 1, 2.5, 3, and 10 μ M was statistically significant with an IC₅₀ of 2.0 μ M. BHS697 hERG inhibition at 0.3, 1, 3, and 10 μ M was statistically significant with an IC₅₀ of 1.2 μ M. CQM157 hERG inhibition at 1, 3, and 10 μ M was statistically significant with an IC₅₀ of 2.7 μ M.

Cardiovascular effects of infigratinib in telemetered dogs were evaluated at doses of 0, 2, 20, and 200 mg/kg using a modified Latin square design. Evaluated parameters included clinical signs, body weight, ECGs, heart rate, arterial blood pressure, body temperature, and clinical chemistry. There were no infigratinib-related changes in ECGs, heart rate, arterial blood pressure, or core body temperature.

Neurological and pulmonary function assessments were done in rats at 10 mg/kg infigratinib. Functional observational battery (FOB) parameters included cage observations, observations during handling, open field observations, sensorimotor function, rectal temperature, grip strength of fore and hind paws, and landing foot splay. Plethysmography parameters included tidal volume, respiratory rate, and minute volume. There were no notable changes observed in the measured parameters at 10 mg/kg.

5.4.ADME/PK

The Applicant's Position:

The pre-clinical drug metabolism and pharmacokinetics (DMPK) of infigratinib have been extensively characterized. The oral bioavailability of infigratinib as a solution was low to medium (1.5% to 51%), consistent with its first-pass clearance. [¹⁴C]-infigratinib was extensively distributed into peripheral tissues in rats after oral and IV doses, including brain, and was specifically taken up into melanin-containing structures in pigmented rats. In vitro, the plasma protein binding of infigratinib across species was high (>96%). Collectively, the in vitro data support that infigratinib is extensively metabolized, primarily by CYP3A4 (~94%) with a partial

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

contribution by FMO3 (6%) and very minor contributions by CYP2D6, CYP2J2, and CYP1A1/2. In hepatocytes, the main biotransformation pathways of [¹⁴C]-infigratinib observed in all species were N-oxidation (to form BQR917) and N-deethylation (to form BHS697). Formation of CQM157 and other metabolites were minor transformation pathways in hepatocytes. In vivo, absorbed [¹⁴C]-infigratinib was extensively metabolized in male and female rats, dogs, and monkeys. All detected human metabolites were also observed in at least one of the 3 species (rats, dogs, or monkeys). Elimination of drug-related material occurred predominantly via the feces in rats, dogs, and monkeys. After single doses of infigratinib, the steady-state plasma clearance was high with t_{1/2} values of 1.47 hr to 5.2 hr across species and route of administration. The PK of the metabolites was characterized in the rat and dog toxicology studies and in pregnant rats and rabbits as part of the embryofetal-development studies. There were no relevant differences in infigratinib systemic exposure between males and females across species. Accumulation in exposure to infigratinib or metabolites after multiple daily doses of infigratinib was <2 to 3-fold across species and studies. In pregnant rabbits, significant accumulation of infigratinib, BHS697, and BQR917 was observed on DG 19 relative to DG 7 (and less than 3-fold accumulation for CQM157).

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

	Major Findings																																				
Absorption RD-2006-01894, 0900385, 0800707, 1300399, 0770963-01, 0610059, 0770100, 0870299, 1270617	- Infigratinib absorption time ranged from 0.5 to 9.5 hr post-dose across species - The bioavailability (F) ranged from 1.5% to 51% across species																																				
Distribution 1300282, 0800423, 0800707, 1300098	- Brain-to-plasma ratio of 0.68 (based on AUC_{0-inf}) - Plasma protein binding of [14C]-BGJ398 using equilibrium dialysis <table><tr><th>Species</th><th colspan="2">Plasma Protein Binding (%)</th></tr><tr><td></td><td colspan="2">10-10000 ng/mL</td></tr><tr><td>Mouse</td><td colspan="2">95.2-98.8</td></tr><tr><td>Rat</td><td colspan="2">95.4-98.3</td></tr><tr><td>Dog</td><td colspan="2">94.4-98</td></tr><tr><td>Human</td><td colspan="2">93.3-98.2</td></tr></table> - In vitro blood distribution study with [14C]-BGJ398 from 10 to 10000 ng/mL <table><tr><th>Species</th><th>Blood-to-Plasma Ratio</th><th>Blood Cells-to-Plasma Ratio</th></tr><tr><td></td><td>10-10000 ng/mL</td><td>10-10000 ng/mL</td></tr><tr><td>Mouse</td><td>1.39-0.85</td><td>1.93-0.65</td></tr><tr><td>Rat</td><td>0.78-0.92</td><td>0.46-0.82</td></tr><tr><td>Dog</td><td>0.99-1.04</td><td>0.98-1.07</td></tr><tr><td>Human</td><td>1.18-0.91</td><td>1.4-0.81</td></tr></table> - Quantitative whole-body autoradiography study after a single oral dose of [14C]-BGJ398 in male pigmented rats (ten highest)	Species	Plasma Protein Binding (%)			10-10000 ng/mL		Mouse	95.2-98.8		Rat	95.4-98.3		Dog	94.4-98		Human	93.3-98.2		Species	Blood-to-Plasma Ratio	Blood Cells-to-Plasma Ratio		10-10000 ng/mL	10-10000 ng/mL	Mouse	1.39-0.85	1.93-0.65	Rat	0.78-0.92	0.46-0.82	Dog	0.99-1.04	0.98-1.07	Human	1.18-0.91	1.4-0.81
Species	Plasma Protein Binding (%)																																				
	10-10000 ng/mL																																				
Mouse	95.2-98.8																																				
Rat	95.4-98.3																																				
Dog	94.4-98																																				
Human	93.3-98.2																																				
Species	Blood-to-Plasma Ratio	Blood Cells-to-Plasma Ratio																																			
	10-10000 ng/mL	10-10000 ng/mL																																			
Mouse	1.39-0.85	1.93-0.65																																			
Rat	0.78-0.92	0.46-0.82																																			
Dog	0.99-1.04	0.98-1.07																																			
Human	1.18-0.91	1.4-0.81																																			

	<table><tr><th>Tissue</th><th>T_{max}</th><th>Mean Rat Tissue Concentration</th></tr><tr><td></td><td>(h)</td><td>(nmol/g)</td></tr><tr><td>Eye Ciliary Body</td><td>48</td><td>49.2</td></tr><tr><td>Bile</td><td>3</td><td>48.9</td></tr><tr><td>Eye Choroid</td><td>48</td><td>32.4</td></tr><tr><td>Adrenal Cortex</td><td>3</td><td>26.2</td></tr><tr><td>Oral Mucosa</td><td>3</td><td>30.3</td></tr><tr><td>Liver</td><td>3</td><td>19.5</td></tr><tr><td>Cecum</td><td>8</td><td>14.9</td></tr><tr><td>Small Intestinal Wall</td><td>3</td><td>11.8</td></tr><tr><td>Preputial Gland</td><td>8</td><td>11.5</td></tr><tr><td>Kidney CM Junction</td><td>3</td><td>10.9</td></tr></table>	Tissue	T _{max}	Mean Rat Tissue Concentration		(h)	(nmol/g)	Eye Ciliary Body	48	49.2	Bile	3	48.9	Eye Choroid	48	32.4	Adrenal Cortex	3	26.2	Oral Mucosa	3	30.3	Liver	3	19.5	Cecum	8	14.9	Small Intestinal Wall	3	11.8	Preputial Gland	8	11.5	Kidney CM Junction	3	10.9									
Tissue	T _{max}	Mean Rat Tissue Concentration																																												
	(h)	(nmol/g)																																												
Eye Ciliary Body	48	49.2																																												
Bile	3	48.9																																												
Eye Choroid	48	32.4																																												
Adrenal Cortex	3	26.2																																												
Oral Mucosa	3	30.3																																												
Liver	3	19.5																																												
Cecum	8	14.9																																												
Small Intestinal Wall	3	11.8																																												
Preputial Gland	8	11.5																																												
Kidney CM Junction	3	10.9																																												
Metabolism 0800499	Metabolite profiling in rat, dog, and human hepatocyte incubations with [¹⁴C]-BGJ398 <table><tr><th>Metabolite M</th><th colspan="3">Percent of BGJ398 Total Radioactivity (%) in Cryopreserved Hepatocytes</th></tr><tr><td></td><th>Human</th><th>Dog</th><th>Rat</th></tr><tr><td>BGJ398</td><td>55</td><td>1.1</td><td>59.4</td></tr><tr><td>M1 (BQR917)</td><td>2.8</td><td>84.8</td><td>2.8</td></tr><tr><td>M2 (BQR246)</td><td></td><td>1.2</td><td>0.9</td></tr><tr><td>M3 (BHS697) (M4)</td><td>17.4</td><td>0.5</td><td>9.4</td></tr><tr><td>M5, M6</td><td>1.9</td><td>2</td><td>2</td></tr><tr><td>M7 – M9</td><td>8.1</td><td>0.4</td><td>6.4</td></tr><tr><td>M10, M11</td><td>2.1</td><td></td><td>1.6</td></tr><tr><td>M12</td><td>3.6</td><td></td><td>0.8</td></tr><tr><td>Pellet</td><td>4.7</td><td>4.6</td><td>4.2</td></tr></table>	Metabolite M	Percent of BGJ398 Total Radioactivity (%) in Cryopreserved Hepatocytes				Human	Dog	Rat	BGJ398	55	1.1	59.4	M1 (BQR917)	2.8	84.8	2.8	M2 (BQR246)		1.2	0.9	M3 (BHS697) (M4)	17.4	0.5	9.4	M5, M6	1.9	2	2	M7 – M9	8.1	0.4	6.4	M10, M11	2.1		1.6	M12	3.6		0.8	Pellet	4.7	4.6	4.2	
Metabolite M	Percent of BGJ398 Total Radioactivity (%) in Cryopreserved Hepatocytes																																													
	Human	Dog	Rat																																											
BGJ398	55	1.1	59.4																																											
M1 (BQR917)	2.8	84.8	2.8																																											
M2 (BQR246)		1.2	0.9																																											
M3 (BHS697) (M4)	17.4	0.5	9.4																																											
M5, M6	1.9	2	2																																											
M7 – M9	8.1	0.4	6.4																																											
M10, M11	2.1		1.6																																											
M12	3.6		0.8																																											
Pellet	4.7	4.6	4.2																																											
Excretion 0800707	Mass balance study in rats after a single intravenous or oral dose of [¹⁴C]-BGJ398 <table><tr><th></th><th colspan="4">[¹⁴C]-BGJ398 Recovery (%)</th></tr><tr><td></td><th>Bile</th><th>Urine</th><th>Feces</th><th>Cage Rinse/Wash</th></tr><tr><td>IV</td><td></td><td>6.5</td><td>91.1</td><td>0.5</td></tr><tr><td>Oral</td><td></td><td>2.1</td><td>97.2</td><td>0.3</td></tr><tr><td>IV (bile duct-cannulated)</td><td>56.6</td><td>16.4</td><td>19.5</td><td>2.1</td></tr></table>		[¹⁴ C]-BGJ398 Recovery (%)					Bile	Urine	Feces	Cage Rinse/Wash	IV		6.5	91.1	0.5	Oral		2.1	97.2	0.3	IV (bile duct-cannulated)	56.6	16.4	19.5	2.1																				
	[¹⁴ C]-BGJ398 Recovery (%)																																													
	Bile	Urine	Feces	Cage Rinse/Wash																																										
IV		6.5	91.1	0.5																																										
Oral		2.1	97.2	0.3																																										
IV (bile duct-cannulated)	56.6	16.4	19.5	2.1																																										

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The nonclinical safety profile of infigratinib has been well characterized in rats and dogs. After 26 or 39 weeks of infigratinib administration in rats and dogs, respectively, the main target organ was bone. When infigratinib was administered to rats and/or dogs for ≤13 weeks the important toxicities included changes in calcium/phosphorus homeostasis, ectopic tissue mineralization in multiple tissues, changes in the cornea, bone, epithelial tissues, teeth, and/or hair/skin. Reversibility was established for all infigratinib-related target organ toxicities with exception of incisor teeth, hair coat changes, and ectopic tissue mineralization (partially reversible at some dose levels/dosing durations). Most, if not all, of the findings were likely due

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

to the pharmacological activity of infigratinib (inhibition of FGFR1-3). Infigratinib was not genotoxic, but did cause embryo and fetal abnormalities in developmental studies. The safety margins at all dose levels was <1 based on a comparison of C_{max} or AUC values in rat and dog toxicity studies to the human exposure (6284 ng*hr/mL; Cycle 1, Day 15) at the recommended dose of 125 mg QD, reflecting the greater sensitivity of the nonclinical species in the toxicology program to the pharmacologic effects (ie, inhibition of FGFR1-3) of infigratinib. The overall toxicity profile of infigratinib includes mechanism-related findings that can be monitored and/or are considered clinically manageable in the intended patient population.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

Study title / number: A 26-Week Oral Gavage Toxicity Study in Rats with a 8-Week Recovery Period / 2821-001

- Dose-dependent centrilobular vacuolation and mild focal necrosis in liver
- Bone toxicities: Dose-dependent decreases in bone strength, decreases in total bone mineral density of femur, decreases in bone strength at the lumbar vertebral body (L4 and L5) in males at >1 mg/kg/day (partially reversible during recovery period)

Conducting laboratory and location: Contract laboratory

GLP compliance: Yes

Group No.	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Animals	
				Males	Females
Main Study					
1	0	0	5	20 ^a	20 ^a
2	0.3	0.06	5	15	15
3	1	0.2	5	15	15
4	3	0.6	5	20 ^a	20 ^a
Toxicokinetic					
5	0	0	5	3	3
6	0.3	0.06	5	6	6
7	1	0.2	5	6	6
8	3	0.6	5	6	6

^a Five animals/sex/group remained on study for an 8-week recovery period.

Excerpted from Applicant's Submission

Methods

Dose and frequency of dosing: 0, 0.3, 1, or 3 mg/kg; once daily for 26 weeks

Route of administration: Oral gavage

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Formulation/Vehicle:	BGJ398 phosphate salt / Acetic Acid-acetate buffer solution, pH 4.6, and polyethylene glycol 300 (PEG300) at 50:50 (v/v)
Species/Strain:	Wistar Han [CrI:WI(Han)] Rats
Number/Sex/Group:	Main Groups: Control and HD (3 mg/kg/day): 20/sex/group with 5/sex/group remaining for 6-week recovery period; LD (0.3 mg/kg/day) and MD (1 mg/kg/day): 15/sex/group
Age:	7.5 weeks to 8 weeks old
Satellite groups/ unique design:	Toxicokinetics: 6/sex/group dosing animals, 3/sex/group controls
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	One control female found dead on Day 180, not associated with test article. One TK female died after blood collection on Day 182, considered procedural-related.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology/Coagulation	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology	Adequate battery: Yes

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Findings	Sex		M				R		F			R	
Daily Dose	(mg/kg)		0	0.3	1	3	3		0	0.3	1	3	3
# of animals			15	15	15	15	5		15	15	15	15	5
Epididymis	Germ cell debris, Increased, bilateral	Minimal				1							
Esophagus	Dilation	Moderate		1									
Heart	Necrosis/infiltrate	Minimal	3	7	6	8			4	2	2	3	
		Mild	1		1	1	1						
Kidneys													
	Hyperplasia, urothelial	Minimal				1				1			
	Hyperplasia, interstitial cell	Minimal								1			
	Nephropathy, chronic progressive	Mild	1	2	2	1							
	Pyelitis	Minimal				1				1			
Liver	Hyperplasia, bile duct	Minimal	3	2		2	1		3	3	5		
	Infiltration, mononuclear cell	Mild				1							
	Necrosis, focal	Minimal	4	3	4	4			1	2		1	
		Mild	1	3	3	1	1		1		1		1
	Vacuolation, centrilobular	Minimal	1	5	5	8	2			1			2
	Infiltration, mixed leukocyte	Mild		1									
	Cyst, biliary	Mild											1
Lung	Histiocytosis, alveolar	Minimal	2	4	1	4			2	1	2	4	
	Infiltration, mixed leukocyte	Minimal		1	1	1							
Pancreas	Hemorrhage/pigment/inflammation/fibrosis, islets	Minimal				3							
	Infiltration, mononuclear cell	Minimal										1	
Testes	Degeneration/Atrophy Seminiferous tubules, bilateral	Minimal				1							

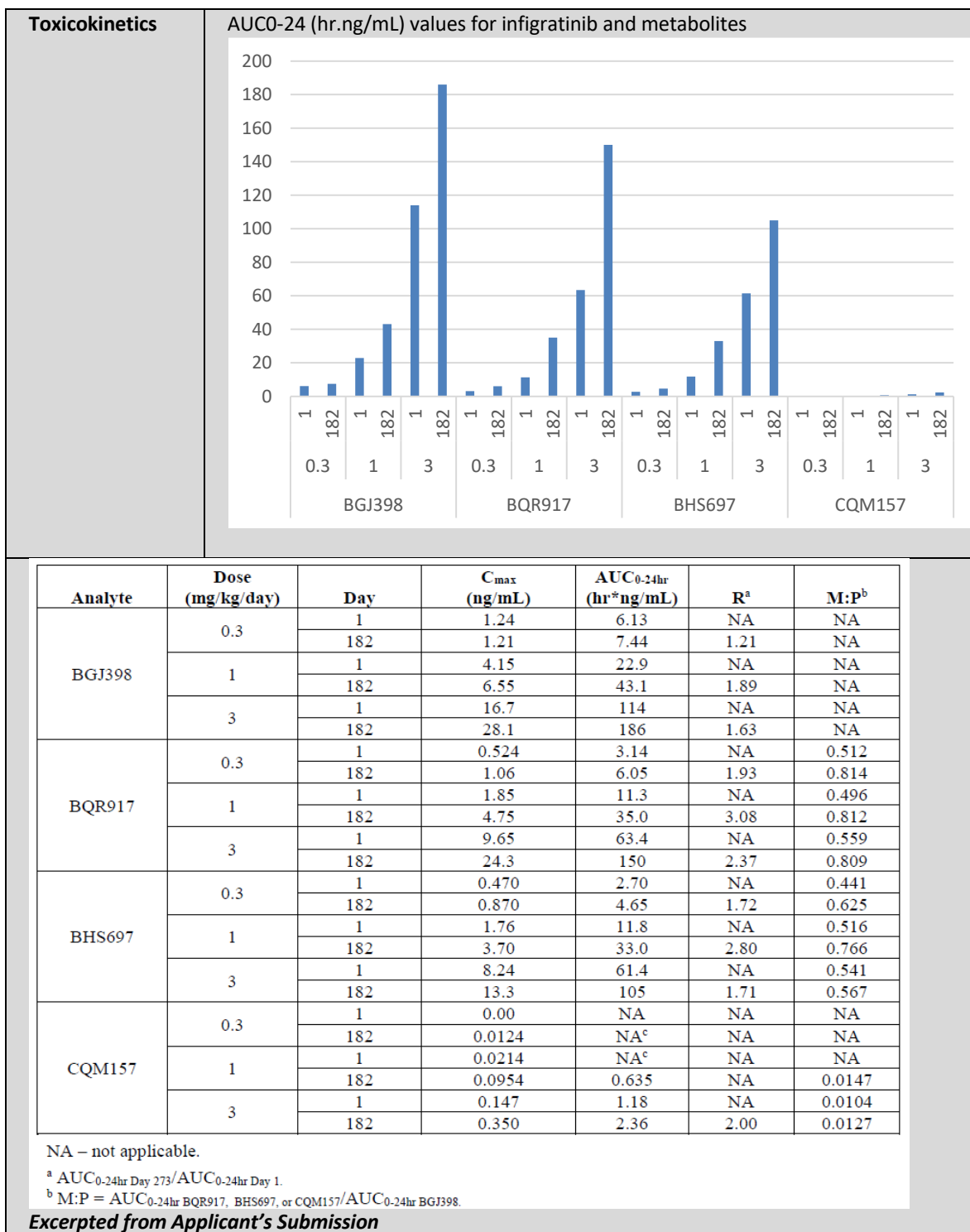
NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Findings		Sex	M				R	F				R
Daily Dose	(mg/kg)		0	0.3	1	3	3	0	0.3	1	3	3
Right femur, Distal Metaphysis Site												
Trabecular pQCT	BMC (mg/mm)		1.2	-6	-16	-24	-41	0.8	-12	-18	3	
	BMD (mg/cm3)		178	-3	-14	-22	-36	257	-12	-14	5	
Right femur, Diaphysis Site												
pQCT	Total Area (mm2)		12.3	-3	-5	-5	-7	8.5		-5	-3	+9
	Cortical Area (mm2)		8.8	-3	-4	-7	-11	6.2		-7	-5	
	Cortical BMC (mg/mm)		11.9	-2	-5	-8	-11	8.4	-2	-7	-5	+5
	Cortical CSMI (mm4)		7.5	-7	-7	-11	-12	3.8		-9	-6	+31
L5 Vertebral Body (Main Study)												
pQCT	Total Area (mm2)		7.3		2	-3		5.8		-5	-3	+12
	Total BMC (mg/mm)		5	-4	-8	-11	-17	4.3	-5	-15	-11	+13
	Total BMD (mg/cm3)		685	-3	-10	-8	-17	747	-7	-10	-8	
Trabecular pQCT	BMC (mg/mm)		0.8	-17	-31	-13	-48	0.6	-10	-16	-14	
	BMD (mg/cm3)		288	-18	-33	-10	-49	338	-12	-11	-12	-10

pQCT- peripheral quantitative computed tomography; BMC-bone mineral content; BMD-bone mineral density; CSMI-cross-sectional moment of inertia

Additional correlation analysis on vertebral body compression at the lumbar vertebrae L4 and/or L5 showed shift between bone mass and strength indicating that BGJ398 administration correlated with decreases in bone strength (0.57 for control males to 0.86 for males at 1 mg/kg/day), consistent with the decrease in total bone mineral density.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)



Study title / number: BGJ398: A 39-Week Oral Gavage Toxicity Study in Dogs with a 13-Week Recovery Period / 2821-002

Bone toxicities: High dose (HD) (3 mg/kg/day) in both sexes had increased growth plate thickness and fractures in the lumbar spine associated with increased physal thickness, focal mixed reaction, and/or bone loss

Conducting laboratory and location: Contract laboratory
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0.3, 1, or 3 mg/kg; once daily for 39 weeks
Route of administration: Oral gavage
Formulation/Vehicle: BGJ398 phosphate salt / Acetic acid-acetate buffer solution, pH 4.6, and polyethylene glycol 300 (PEG300) at 50:50 (v/v)
Species/Strain: Beagle dogs
Number/Sex/Group: 6/sex/dose for 0 and 3 mg/kg/day; 4/sex/dose for 0.3 and 1 mg/kg/day
Age: ~ 6 months old at the initiation of dosing
Satellite groups/ unique design: None
Deviation from study protocol affecting interpretation of results: No

Observations and Results:

Parameters	Major findings									
Mortality	One female at LD (0.3 mg/kg/day) was euthanized in extremis on Day 204 due to severe salivation, decreased activity, red discharge from mouth, audible breathing, coughing, abnormal lung sounds, and severely increased respiratory effort. Microscopically, the lungs had large areas of hemorrhage potentially associated with inflammation, and death was attributed to respiratory distress, considered unrelated to infigratinib administration.									
Clinical Signs	Unremarkable									
Body Weights	Unremarkable									
Ophthalmoscopy	Unremarkable									
ECG	Unremarkable									
Hematology	Unremarkable									
Clinical Chemistry	Sex	Days	M				F			
	Dose (mg/kg)		0	0.3	1	3	0	0.3	1	3
	Calcium (mg/dL)	273	10.41	10.35	10.24	10.29	10.24	110.37	10.26	10.30
		362	10.22			9.81	10.20			9.87
	Phosphorus (mg/dL)	273	4.36	4.80	4.46	4.83	3.68	4.61	4.02	4.65
		362	4.08		4.19		3.40			3.76

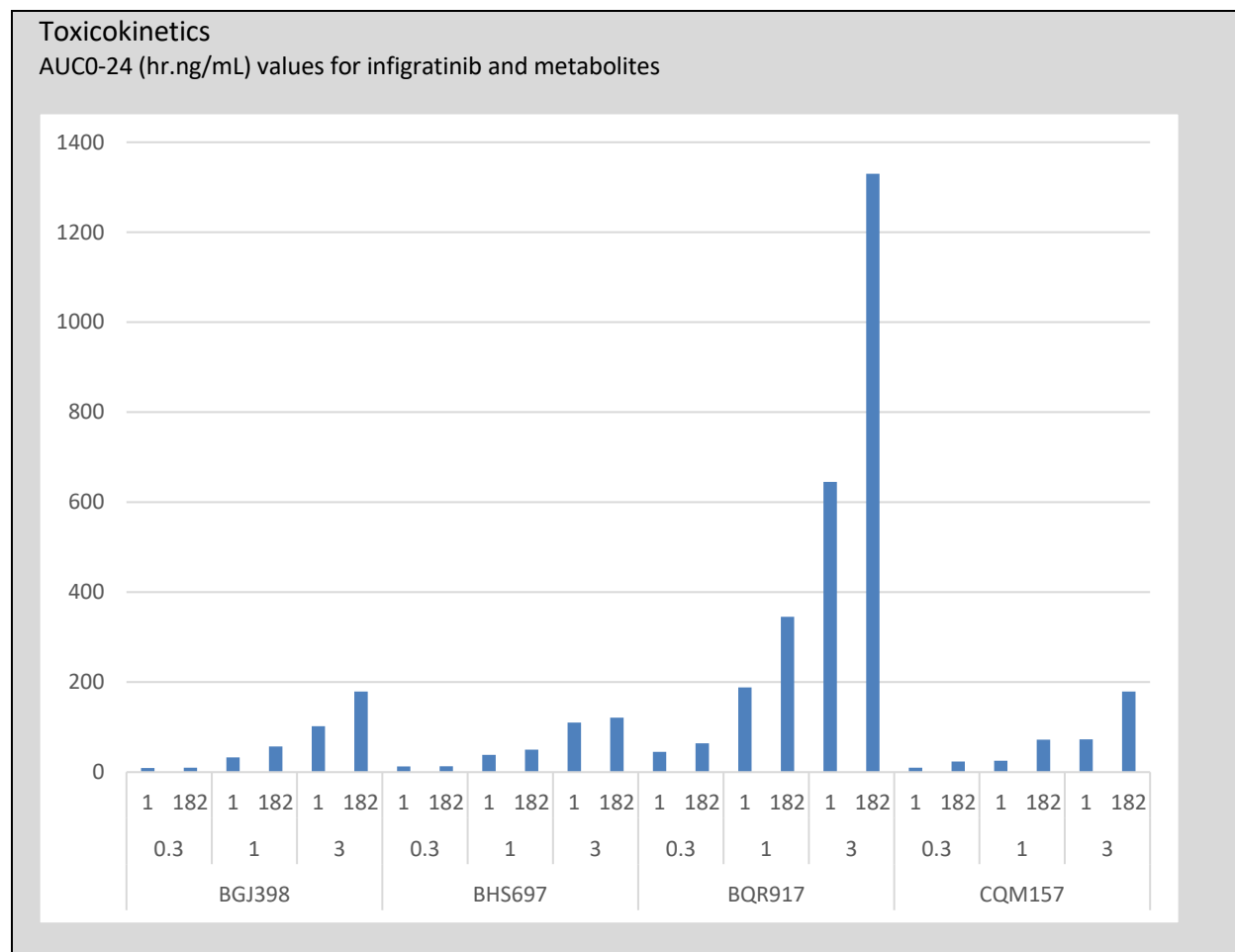
NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Urinalysis	Unremarkable									
Gross Pathology	Unremarkable									
Organ Weights	Unremarkable									
Histopathology	Adequate battery: Yes									
Findings	Sex		M				F			
Daily Dose	(mg/kg)		0	0.3	1	3	0	0.3	1	3
# of animals			4	4	4	4	4	4	4	4
Aorta	Mineralization	Mild							1	
Brain	Infiltration, mononuclear cells	Minimal		1	1			1		
	Infiltration, mixed cells, perivascular	Minimal		1						
	Mineralization, focal	Minimal						1		
Epididymis	Inflammation, perivascular/vascular	Minimal			1					
Joint	Hyperplasia/hypertrophy, synovial	Minimal		1						
	Inflammation, subacute/chronic	Minimal		1						
Skeletal muscle	Regeneration	Minimal		1						
Skin	Erosion/ulcer	Moderate				1				
	Inflammation, hair follicle/epidermis	Minimal								1
Thymus	Decreased lymphocytes, generalized	Minimal	3	2	1	1	3	2	2	1
		Mild	1	2	3	2	1	1	2	2
		Moderate				1				
Vertebrae	Fracture/callus	Mild				2				2
	Increased thickness, growth plate	Mild				2				3
		Moderate				1				
Kidneys	Mineralization	Minimal						1		
	Infiltration, mononuclear cell	Mild								
	Vacuolation	Mild								1
Large intestine, rectum	Dilatation/inflammation, mucosal gland	Mild							1	
		Minimal							1	
	Infiltration, subacute/chronic	Minimal						1	1	1
Liver	Infiltration, mononuclear cells	Minimal						1	1	
Lung	Inflammation, granulomatous	Minimal						1		
	Granuloma	Minimal						1		
No findings in recovery animals.										

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

Bone Evaluations (radiographic)	Bone Findings				
	Sex		M	F	
	Dose (mg/kg)		3	3	
	Bone Alkaline Phosphatase	% compared to controls	-13	+25	
	Vertebrae	Fracture/callus	Mild	2/4	2/4
	Vertebrae/growth plate	Increased thickness	Mild	2/4	3/4
			Moderate	1/4	
	2/4 = 2 animals affected out of 4 assessed				

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)



NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Analyte	Dose (mg/kg/day)	Day	C _{max} (ng/mL)	AUC _{0-24hr} (hr*ng/mL)	R ^a	M:P ^b
BGJ398	0.3	1	1.22	8.87	NA	NA
		273	1.95	9.77	1.27	NA
	1	1	2.81	32.5	NA	NA
		273	6.56	56.8	1.80	NA
	3	1	7.85	102	NA	NA
		273	12.8	179	1.85	NA
BQR917	0.3	1	5.36	44.8	NA	5.03
		273	13.5	64.0	1.70	6.46
	1	1	17.4	188	NA	5.86
		273	48.5	345	1.90	6.28
	3	1	54.5	645	NA	6.39
		273	125	1330	2.12	7.64
BHS697	0.3	1	0.866	12.3	NA	1.48
		273	1.18	12.9	1.04	1.39
	1	1	2.46	38.0	NA	1.15
		273	3.03	49.8	1.37	0.900
	3	1	6.43	110	NA	1.10
		273	7.06	121	1.14	0.688
CQM157	0.3	1	0.596	9.54	NA	1.26
		273	1.53	23.2	2.68	2.55
	1	1	1.58	25.2	NA	0.823
		273	3.96	71.8	2.83	1.35
	3	1	4.40	72.5	NA	0.742
		273	11.3	179	2.60	1.06

NA – not applicable.
^a R = AUC_{0-24hr} Day 273/AUC_{0-24hr} Day 1.
^b M:P = AUC_{0-24hr} BQR917, BHS697, or CQM157/AUC_{0-24hr} BGJ398.

Excerpted from Applicant's Submission

General toxicology; additional studies (summary)

13-Week Toxicity Study with a 6-Week Recovery in Wistar Han Rats (Study number: 1270617)

The phosphate salt of infigratinib, in a formulation containing acetic acid/acetate buffer pH 4.68 and PEG300, was administered orally (gavage) to male and female rats (20/sex/group) at doses of 0 (vehicle control), 1, 3, or 10 mg/kg/day. Recovery animals (10/sex/group) were administered 0, 3, or 10 mg/kg/day infigratinib. Blood samples were collected for an evaluation of systemic exposure of infigratinib and its metabolites BHS697 and BQR917 (Weeks 1, 6, and 12).

Observation and Results (fold changes with respect to controls):

- Dose-dependent clinical signs at ≥3 mg/kg/day included a prominent backbone; at 10 mg/kg/day there were animals with thin body condition.
- Teeth toxicities included an increased incidence of broken incisor, with microscopic findings of incisor teeth degeneration at 10 mg/kg/day with a translucent appearance. Maxillary and mandibular incisors were characterized by near complete degeneration of the enamel organ

resulting in an absence of enamel formation, collapse of enamel space, and absence of the ameloblast layer. In some regions, fracture of incisors was associated with thinning and/or fragmentation of dentin, a slight decrease in cellularity of the odontoblast layer, and replacement by interstitial cells and new bone proliferation. These changes were not noted in molars. Macroscopic findings of small, discolored, and/or fractured maxillary and mandibular incisors were not recoverable at 10 mg/kg/day.

- Ocular toxicities: Corneal opacity was noted at pre-treatment in almost all animals; however, increased severity in corneal opacity in males at 10 mg/kg/day was observed at Week 4 and included both sexes by Week 13. Microscopically, corneal opacity correlated with keratopathy and corneal mineralization. Decreased severity of ocular opacity was observed after the 6-week recovery period, but there was no reversibility for microscopic ocular mineralization at 10 mg/kg/day.

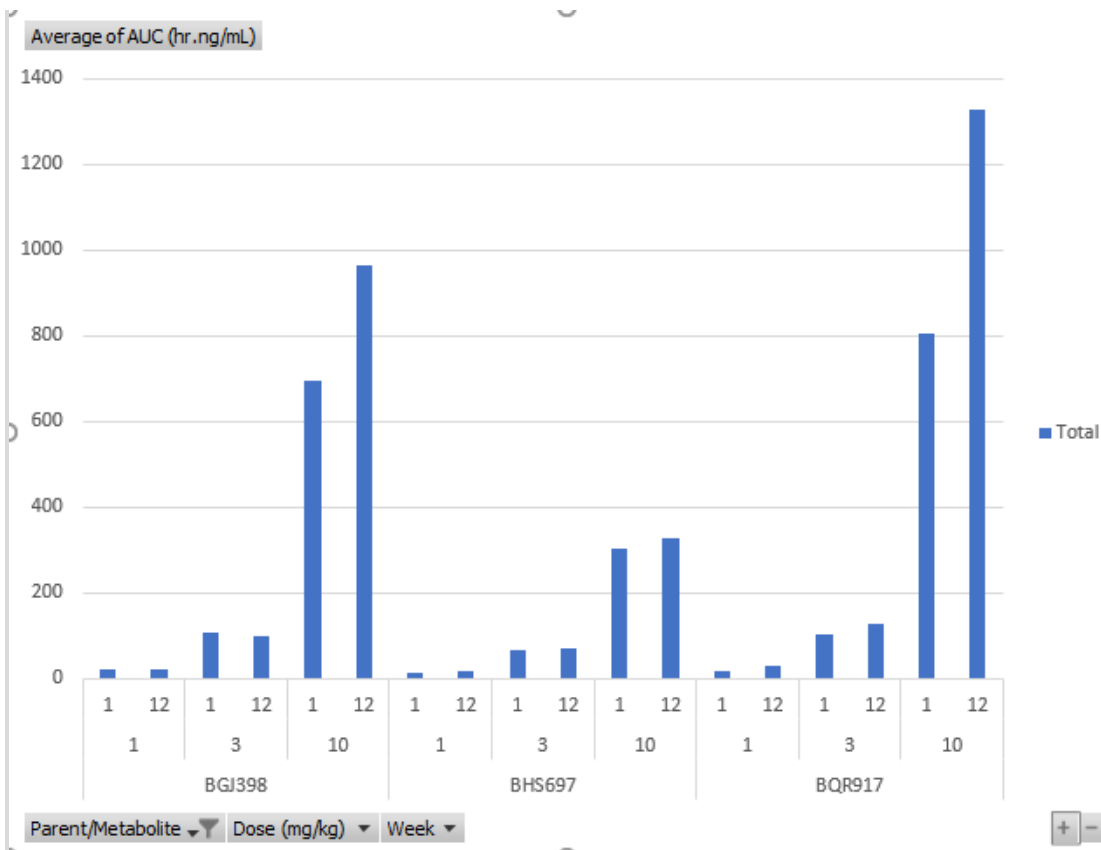
13-Week Rat Findings in Eye		M		F	
BGJ398 Dose (mg/kg/day)		0	3	10	10
# Examined Animals		20	19	20	19
Keratopathy, cornea					
	Minimal		1		2
	Mild			15	14
	Moderate			5	5
Mineralization, corneal (focal/multifocal)					
	Minimal	2		3	4
	(R=Recovery animals)			(1/10 R)	(3/10 R)
	Mild			2	(1/10 R)

- A change in coat appearance (longer hair) and abnormal appearance of skin upon microscopic observation was noted in animals at 10 mg/kg/day from Week 8 to the end of the recovery period.
- Bone toxicities: dose-dependent infigratinib-related microscopic findings observed in femur and sternum (growth plate thickening), hard palate (decreased thickness epithelium) at ≥ 3 mg/kg/day, and nasal cavity (cartilage hypertrophy) at 10 mg/kg/day.
- Dose-dependent infigratinib-related microscopic findings were observed in kidney (mineralization) and tongue (decreased thickness of epithelium) at 10 mg/kg/day.
- Increases in AST (female 10 mg/kg/day: +1.44-fold, Week 12), ALP (female 10 mg/kg/day: +1.77-fold, Week 5), and phosphorus (female 10 mg/kg/day: +38%, Week 12) and changes in urea (+14%) and creatinine (+17%), consistent with kidney toxicity (e.g., mineralization).
- Alveolar macrophages were noted in the lungs of some animals at 3 and 10 mg/kg/day and persisted to the end of the recovery.
- Biomarker fibroblast growth factor 23 (FGF23): Plasma FGF23 levels were elevated in males and females at 10 mg/kg/day in the 5 and 13-week samples. (The highest values at Week 13: males at 10 mg/kg/day: +6.9-fold; females at 10 mg/kg/day: +4.2-fold)

Toxicokinetics

AUC₀₋₂₄ values for infigratinib and metabolites

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)



NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

13-Week Oral Gavage Toxicity Study of BGJ398 in Rat (CQM157 not quantified in any of samples)									
Daily dose	1 (mg/kg/day)			3 mg/kg/day			10 mg/kg/day		
# Animals	M (20)	F (20)	Mean	M (20)	F (20)	Mean	M (20)	F (20)	Mean
BGJ398									
AUC ₀₋₂₄ (ng.hr/mL)									
Week 1	18.8	26.6	22.7	61.3	151	106.1	399	991	695
Week 12	18.9	26.9	22.9	75.4	123	99.2	751	1180	965.5
C _{max} (ng/mL)									
Week 1	3.69	4		8.95	19.6		48.9	120	
Week 12	2.88	3.82		8.69	12.3		74.7	100	
T _{max} (h)									
Week 1	3	3		1	3		3	3	
Week 12	3	3		3	3		3	7	
BQR917									
AUC ₀₋₂₄ (ng.hr/mL)									
Week 1	14.5	22.2	18.3	56.5	148	102.2	431	1180	805.5
Week 12	17.7	39.6	28.6	94.3	164	129.1	952	1700	1326
C _{max} (ng/mL)									
Week 1	2.9	3.5		6.2	17.3		57.3	139	
Week 12	3	4.2		10.8	15.2		92.4	148	
T _{max} (h)									
Week 1	3	3		3	3		3	3	
Week 12	3	3		3	7		3	3	
BHS697									
AUC ₀₋₂₄ (ng.hr/mL)									
Week 1	15.1	10.2	12.65	58.6	74	66.3	237	367	302
Week 12	23.6	8.95	16.27	82.3	57.2	69.75	349	308	328.5
C _{max} (ng/mL)									
Week 1	2.27	1.67		5.58	8.25		24.1	37	
Week 12	2.55	1.59		6.76	5.41		31	23	
T _{max} (h)									
Week 1	3	3		7	7		7	3	
Week 12	3	3		7	3		3	3	
BGJ398+ BHS697+ BQR917									
AUC ₀₋₂₄ (ng.hr/mL)									
Week 1	48.4	59	53.7	176.4	373	274.7	1067	2538	1802.5
Week 12	60.2	75.4	67.8	252	344.2	298.1	2052	3188	2620

13-Week Toxicity Study with a 6-Week Recovery in Beagle Dogs (Study number: 1270616)

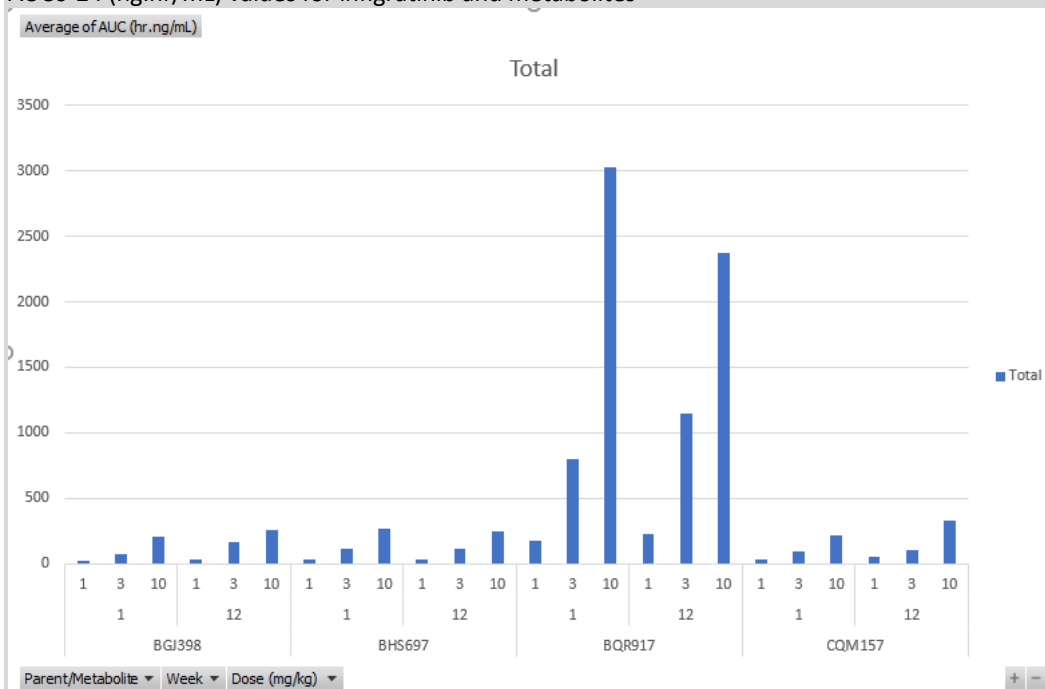
The phosphate salt of infigratinib, in a formulation containing a mixture of acetic acid/acetate buffer and PEG300, was administered orally (gavage) to male and female dogs (4/sex/group) at doses of 0 (vehicle control), 1, 3, or 10 mg/kg/day. Recovery animals (2/sex/group) were administered 0 or 10 mg/kg/day infigratinib. Blood samples were collected for an evaluation of systemic exposure of infigratinib and its metabolites CQM157, BQR917, and BHS697 (Week 1, 6, and 12). Evaluated parameters included clinical signs, body weight, food consumption, clinical pathology (hematology, clinical chemistry, coagulation, and urinalysis), ophthalmic exams, ECGs, organ weights, and macroscopic and microscopic examinations. FGF23 levels were also measured.

Observation and Results (fold changes with respect to controls):

- GI-related clinical signs (inappetence, partially digested food, liquid feces) resulted in recoverable decreases in mean body weight gains and food consumption at 10 mg/kg/day in males.
- Increased eosinophils (Weeks 9 and 12) and increased fibrinogen (Week 12) in males at 10 mg/kg/day
- Increased ALT (highest fold increases in Week 9 males at 10 mg/kg/day: +9.11-fold), AST (highest increases in females at 10 mg/kg/day: +1.51-fold), ALP (highest increases in Week 12 females at 3 mg/kg/day: +2.45-fold), and phosphorus in females (Week 9: +30%) and males (Week 5: +38%) at 10 mg/kg/day. Findings were recoverable.
- Bone toxicities: Microscopic changes in bone (sternal bone minimal/mild growth plate thickening) at 1 mg/kg/day and above.
- Microscopic findings of minimal acinar atrophy and duct dilatation of meibomian glands occurred at or above 3 mg/kg/day were partially reversible.
- Skin toxicities: Sebaceous glands in skin (minimal acinar atrophy) and minimal hyperkeratosis of inguinal/mammary gland occurred at 10 mg/kg/day and were fully reversible.
- Biomarker fibroblast growth factor 23 (FGF23): the highest increases noted in males at 10 mg/kg/day on Week 5: +1.9-fold; females at 10 mg/kg/day on Week 13: +1.5-fold.

Toxicokinetics

AUC₀₋₂₄ (ng.hr/mL) values for infigratinib and metabolites



NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

13-Week Oral Gavage Toxicity Study of BGJ398 in Dog										
Daily dose		1 (mg/kg/day)			3 mg/kg/day			10 mg/kg/day		
	# Animals	M (4)	F (4)	Mean	M (4)	F (4)	Mean	M (4)	F (4)	Mean
BGJ398										
AUC ₀₋₂₄ (ng.hr/mL)										
Week 1		14.1	22.4	18.25	61.7	81.1	71.4	166	252	209
Week 12		29.6	36.9	33.25	127	195	161	226	285	255.5
C _{max} (ng/mL)										
Week 1		2.75	2.99		6.21	7.78		12.4	23.5	
Week 12		2.63	3.01		10.1	14.8		16.2	20.2	
T _{max} (h)										
Week 1		0.5	1.75		3	1		9.5	2	
Week 12		5	7		7	5		3	5	
BHS697										
AUC ₀₋₂₄ (ng.hr/mL)										
Week 1		32.4	40	36.2	97.6	127	112.3	213	320	266.5
Week 12		30.4	39.6	35	93.2	131	112.1	218	273	245.5
C _{max} (ng/mL)										
Week 1		2.85	3.34		7.22	7.3		12.3	19.3	
Week 12		2.56	2.66		5.84	7.66		11.5	14.7	
T _{max} (h)										
Week 1		2	2		2	4		9.5	7.5	
Week 12		4	5		7	7		9.5	7	
CQM157										
AUC ₀₋₂₄ (ng.hr/mL)										
Week 1		42	32.6	37.3	72.4	114	93.2	161	279	220
Week 12		41.2	56.7	48.95	85.7	132	108.8	295	361	328
C _{max} (ng/mL)										
Week 1		2.38	1.98		4.72	7.02		11.2	17	
Week 12		2.2	2.78		4.8	7.62		14.2	19.7	
T _{max} (h)										
Week 1		12	18		24	24		24	24	
Week 12		4	24		1	12.5		13.5	24	
BQR917										
AUC ₀₋₂₄ (ng.hr/mL)										
Week 1		143	212	177.5	829	776	802.5	2970	3090	3030
Week 12		196	257	226.5	840	1450	1145	2280	2460	2370
C _{max} (ng/mL)										
Week 1		30.7	31.2		117	106		276	331	
Week 12		35.5	35.7		96.4	123		191	207	
T _{max} (h)										
Week 1		0.5	1		1	1		7	2	
Week 12		1	1		0.75	1.75		2	1	
BGJ398+ BHS697+CQM157+BQR917										
AUC ₀₋₂₄ (ng.hr/mL)										
Week 1		231.5	307	269	1060.7	1098.1	1079.4	3510	3941	3725.5
Week 12		299.2	390.2	344.7	1145.9	1908	1526.9	3019	3379	3199

5.5.2. Genetic Toxicology

The Applicant's Position:

Infigratinib showed no evidence of mutagenicity in the in vitro bacterial reverse mutation assay and was not clastogenic in an in vitro human peripheral blood lymphocyte chromosome aberration assay. Furthermore, Infigratinib did not induce micronuclei in polychromatic erythrocytes in an in vivo rat bone marrow micronucleus assay. In conclusion, infigratinib is not considered to be genotoxic.

The major infigratinib metabolite BHS697 showed no structural alerts for mutagenicity in an in silico assessment. CQM157, the other major infigratinib metabolite, was not mutagenic in an in vitro bacterial reverse mutation assay. In conclusion BHS697 and CQM157 are not considered to be genotoxic.

The FDA's Assessment:

FDA agrees with the Applicant's position.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Mutagenicity test using *Salmonella typhimurium* / 0870301

Key Study Findings:

- BGJ398 was not mutagenic

GLP compliance: Yes

Test system: Bacterial Ames test: *Salmonella typhimurium*: TA98, TA97a, TA100, TA102, TA1535; Aroclor-induced rat liver S9 (5% v/v)

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title / number: Induction of chromosome aberration in cultured human peripheral blood lymphocytes / 0870303

Key Study Findings:

- BGJ398 did not induce clastogenicity without S9 to 10 µg/mL, with S9 to 40 µg/mL, or after a 20 hr treatment without S9 to 5 µg/mL.

GLP compliance: Yes

Test system: Chromosome aberration; human PBMC

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title / number: Induction of micronuclei in the bone marrow of treated rats / 1370743

Key Study Findings:

- BGJ398 was not clastogenic.

GLP compliance: Yes

Test system: Induction of bone marrow micronuclei in polychromatic erythrocytes from Wistar Han rats
Study is valid: Yes

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with infigratinib and are not required for the proposed indication.

The FDA's Assessment:

Carcinogenicity studies are not recommended for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility and Early Embryonic Development: In a study of fertility and early embryonic development in Wistar Han rats, once daily infigratinib administration had no effect on mating or fertility in the males, male reproductive organ weights, or sperm motility, density, or morphology in the males. Similarly, infigratinib administration had no effect on estrous cycling parameters in the females or on mating or fertility in the females. Infigratinib adverse treatment-related effects were limited to a decrease in embryo-fetal viability at 3 mg/kg/day.

Embryo-Fetal Development: The potential maternal and embryo-fetal developmental effects of infigratinib after once-daily dosing was evaluated in female Wistar Han rats and female New Zealand White rabbits. Infigratinib adverse treatment-related effects in rats included reductions in maternal body weight, body weight gain, and food consumption at 10 mg/kg/day. Increases in embryo-fetal death, with corresponding reductions in the numbers of viable fetuses, were observed at 10 mg/kg/day, and reductions in mean fetal body weights were observed at 3 and 10 mg/kg/day. Fetal abnormalities were observed at increased incidences at all doses. The NOAEL for maternal toxicity was considered to be 3 mg/kg/day. The NOAEL for developmental toxicity could not be determined (<1 mg/kg/day). The 1 mg/kg/day dose corresponded to DG 17 mean C_{max} and AUC_{0-24hr} exposure values of 3.56 ng/mL and 28.2 ng*hr/mL, respectively. The 3 mg/kg/day dose corresponded to DG 17 mean C_{max} and AUC_{0-24hr} exposure values of 16.5 ng/mL and 165 ng*hr/mL, respectively. In rabbits, maternal morbidity/mortality was observed in all dose groups including control and was likely related to vehicle intolerance. Reductions in fetal body weight were observed at 3 mg/kg/day.

Pre- and Postnatal Development: No pre- or post-natal studies have been conducted with infigratinib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

Fertility and Early Embryonic Development

Study title / number: A Fertility and Early Embryonic Development Study of BGJ398 Phosphate Salt by Oral Administration (Gavage) in Wistar Hannover Rats / Study 20169843

Key Study Findings

- In the embryo-fetal portion of a rat fertility study, infigratinib decreased the mean number of embryos and increased nonviable embryos and post-implantation loss in females at 3 mg/kg/day.

Conducting laboratory and location
GLP compliance:

Contract laboratory
Yes

Methods

Dose and frequency of dosing:

0, 0.3, 1, or 3 mg/kg/day

Male rats: once daily beginning 15 days before cohabitation, during cohabitation, and continuing through the week before euthanasia for a minimum of 35 doses

Female rats: once daily beginning 15 days before cohabitation, during cohabitation, and continuing until gestation day (DG) 7.

Route of administration:

Oral (gavage)

Formulation/Vehicle:

Acetic acid/acetate buffer solution, pH 4.6, and polyethylene glycol 300 (PEG300) at 50:50 (v/v)

Species/Strain:

Wistar Han Rats

Number/Sex/Group:

22/sex/group

Satellite groups:

None

Study design:

Group No.	Test Material	Dose Level (mg/kg)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Animals	
					Males	Females
1	Control	0	0	5	22	22
2	BGJ398	0.3	0.06	5	22	22
3	BGJ398	1	0.2	5	22	22
4	BGJ398	3	0.6	5	22	22

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Body Weights		Unremarkable							
Sex		M				F			
Daily Dose (mg/kg)		0	0.3	1	3	0	0.3	1	3
No. Evaluated		22	22	22	22	22	22	22	22
Sperm morphology	Abnormal (%)	4	3.7	3.9	3.8				
Persistent diestrus	Total								1
Pregnant females	Total					17	16	22	21
Pre-implantation loss	(Mean %)					7.8	10.2	6.7	5.2
Viable embryos	Total					191	168	251	225
	(Mean)					(11.2)	(10.5)	(11.4)	(10.7)
Nonviable embryos	Total					7	5	17	18
	(Mean)					(0.4)	(0.3)	(0.8)	(0.9)
Post-implantation loss	(%)					4.3	3.1	6.6	7.4
Dams with	Nonviable embryos					4	3	11	11
	Viable embryos					17	16	22	21
Necropsy days in males (M): Day 36-39; in females (F) gestation day (GD) 13									

Embryo-Fetal Development

Study title / number: An Embryo-Fetal Development Study of BGJ398 Phosphate Salt by Oral Administration (Gavage) in Rats / 20177191

Key Study Findings

- Once daily oral administration of infigratinib to pregnant rats during organogenesis resulted in an increase in embryo-fetal lethality at 10 mg/kg/day and reductions in fetal body weights at ≥ 3 mg/kg/day (< 0.1 times the human exposure at the clinical dose of 125 mg).
- Fetal abnormalities (external, soft tissue, and skeletal) were increased at ≥ 1 mg/kg/day (< 0.1 times the human exposure at the clinical dose of 125 mg).

Conducting laboratory and location: Contract laboratory
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 1, 3, or 10 mg/kg/day; once daily on Days 7 through 17 of presumed gestation (GD 7 through 17)

Route of administration: Oral gavage

Formulation/Vehicle: BGJ398 phosphate salt; Acetic acid/acetate buffer solution, pH 4.6, and polyethylene glycol 300 (PEG300) at 50:50 (v/v)

Species/Strain: Wistar Han (CrI:WI(Han)) female rats; presumed pregnant

Number/Sex/Group: 20/females/group
3 additional rats in Group 1 (control) and

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

6 rats/group in Groups 2-4 for TK sampling

Satellite groups:

Study design:

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Main Study Animals	No. of Toxicokinetic Study Animals
1	Control	0	0	5	20	3
2	BGJ398	1	0.2	5	20	6
3	BGJ398	3	0.6	5	20	6
4	BGJ398	10	2	5	20	6

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major findings				
Mortality	Unremarkable				
Clinical Signs	Unremarkable				
Daily Dose (mg/kg)	0	1	3	10	
Dams					
No. Pregnant Dams	18	20	20	19	
No. Live Fetuses	18	20	20	14	
No. with Resorptions	9	10	9	18	
No. with All Nonviable				5	
Body Weight Gain (%) Day 7–21				-44	
Body Weight (%) Day 21				-14	
Mean % Pre-implantation Loss	2.1	8.7	5.7	11.2	
Mean No. of Early Resorptions				5.1	
Mean No. of Total Resorptions				5.3	
Litters					
No. of Litters Evaluated	18	20	20	14	
No. of Live Fetuses	183	201	219	109	
Mean No. Resorptions				5.3	
Mean % Pre-implantation Loss	2.1	8.7	5.7	11.2	
Mean % Post-implantation Loss	6.1	9.0	6.3	49.4	
Mean Fetal Body Weight	5.2	5.2	4.9	3.5	
Fetal Sex Ratio (% live males)	46	47	53	56	

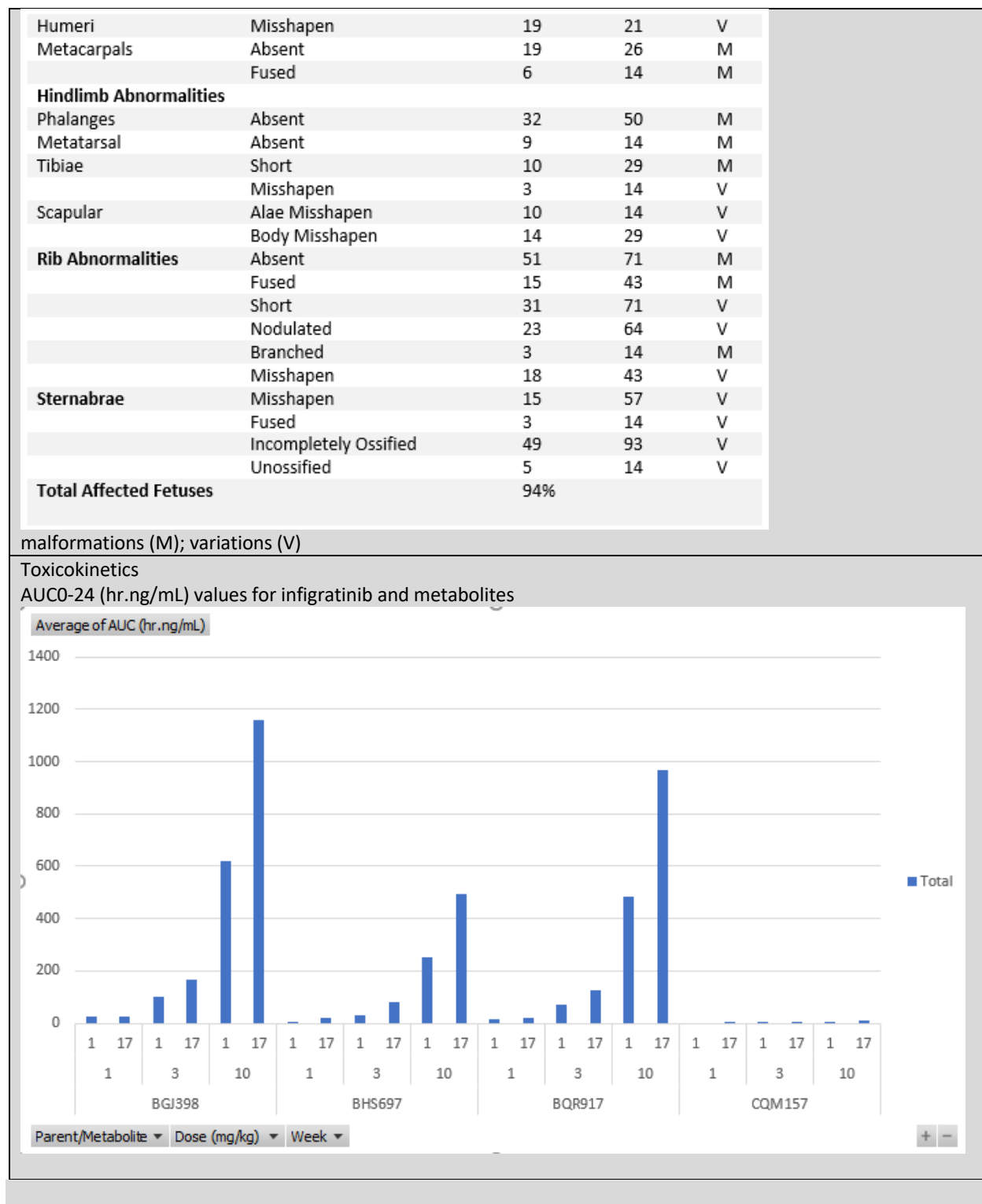
NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

High Dose (10 mg/kg/day)				
Number of evaluated		109	14	
		% Fetuses	% Litters	M/V
Gross External Abnormalities				
Cranio-Facial Defects	Domed head	19	43	M
	Cleft palate	30	57	M
Forepaw/digit Defects	Adactyly	71	93	M
	Brachydactyly	3	14	M
	Syndactyly	7	21	M
Hind paw/digit Defects	Adactyly	22	43	M
	Brachydactyly	5	29	M
	Syndactyly	8	29	M
Tail Malformations	Absent	6	21	M
	Curled	6	21	M
	Short	11	36	M
Trunk Defects	Absent Anus	17	36	M
Total Affected Fetuses		79%		
Fixed Head				
Brain abnormalities	Minimal dilation of lateral ventricles	6	15	V
	Moderate dilation of lateral ventricles	14	31	V
Total Affected Fetuses		23%		
Visceral Abnormalities				
Circulatory system-malposition	Innominate artery	22	39	V
	Subclavian artery	22	39	M
	Malposition			
Gonad Defects	Uterus, narrow	5	15	M
Thymus	Absent	17	31	M
Total Affected Fetuses		57%		

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

High Dose (10 mg/kg/day)		109	14	
Number of evaluated		% Fetuses	% Litters	M/V
Skeletal Abnormalities				
Supraoccipital	Incompletely ossified	46	71	V
Skull Abnormalities				
Nasal bone	Incomplete Ossification	30	43	V
Palatine bone	Incomplete Ossification	38	57	V
Tympanic Annuli	Incomplete Ossification	9	21	V
Vertebral Abnormalities				
Caudal	Vertebrae Absent	4	14	M
	Vertebrae Misaligned	6	21	V
	Vertebrae Unossified	9	29	V
	Vertebrae Incompletely Ossified	26	43	V
Cervical	Vertebrae Arches Misshapen	14	36	V
	Vertebrae Arches Incomplete Ossification	8	21	V
	Hemivertebra	16	36	M
Thoracic	Vertebrae Absent	34	64	M
	Centre	47	79	V
	Incomplete Ossification	7	21	V
	Centre Unossified	15	36	M
Lumbar	Centre, Fused	5	14	M
	Arches, Absent	13	29	V
	Arches, Small	22	36	M
	Arches, Fused	14	29	V
	Arches, Misshapen	10	29	M
	Hemivertebra	33	64	M
	Vertebrae, Supernumerary	16	36	M
	Centre, Fused	39	57	V
	Centre Incomplete Ossification	6.6	14	V
	Centre, Misshapen	22	36	M
Sacrum	Arches, Fused	14	21	V
	Arches, Misshapen	11	21	V
	Centre Unossified	25	36	V
	Centre Incomplete Ossification	14	29	V
	Arches, Misshapen			
Forelimb Abnormalities				
Phalanges	Absent	71	93	M

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)



Study title / number: An Embryo-Fetal Developmental Study of BGJ398 Phosphate Salt by Oral Administration (Stomach Tube) in Rabbits / 20177193 - Key Study Findings

BGJ398 Once daily oral administration of BGJ398 at ≥ 0.3 mg/kg/day to pregnant rabbits resulted in maternal toxicity and a corresponding reductions in fetal body weights

Conducting laboratory and location: Contract laboratory
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0.3, 1, or 3 mg/kg/day once daily GD7–19
Route of administration: Oral, stomach tube
Formulation/Vehicle: BGJ398 phosphate salt; Acetic acid/acetate buffer solution, pH 4.6, and polyethylene glycol 300 (PEG300) at 50:50 (v/v)
Species/Strain: New Zealand White Hra: (NZW)SPF females
Number/Sex/Group: 20 females/group
Satellite groups: None
Study design:

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Main Study Animals	No. of Toxicokinetic Animals
1	Control	0	0	5	20	3
2	BGJ398	0.3	0.06	5	20	3
3	BGJ398	1	0.2	5	20	3
4	BGJ398	3	0.6	5	20	3

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	One female (1/20) was found dead in control, 3/20 at LD, 5/18 pregnant at MD, and 3/19 at HD (3 mg/kg/day)
Clinical Signs	Sign of ungroomed fur increased at LD (11/20) and HD (15/19); Dose-related increase in animals with thin appearance (10/19 at HD)
Body Weights	Dose-dependent effect on body weight gain (highly variable)
Necropsy findings	- Fetal evaluations were based on 129, 126, 57, and 102 fetuses in 15, 15, 7, and 12 litters in the 0 (control), 0.3, 1, and 3 mg/kg/day dose groups, respectively. - Significant BGJ398-related signals for fetal external, soft tissue, or skeletal abnormalities were not noted, with one fetus out of 414 term fetuses being 0.24%): - Control – one fetus with multiple nodulated ribs, incompletely ossified bones in the skull (frontals, mandibles, maxillae, nasals, parietals, premaxillae, tympanic annulae), bent hyoid alae, misshapen squamosals, a misshapen sternebra, and a pair of full supernumerary

	ribs in a cervical vertebra; one fetus with umbilical hernia, malpositioned intestines ○ LD – one fetus with domed head, moderate dilatation in the third ventricle of the brain, both frontals were incompletely ossified ○ HD – one fetus with centrum of the 1st cervical vertebrae malpositioned ventral to the centrum of the 2nd cervical vertebrae, fused ribs (3rd and 4th right ribs and 2nd and 3rd left ribs) and a misshapen 2nd sternebra; one fetus with incomplete ossification in the 12th thoracic centrum, centra in the 12th and 13th thoracic vertebra fused																																																													
Necropsy findings	EFD in Rabbits <table><tr><td>Daily Dose (mg/kg)</td><td>0</td><td>0.3</td><td>1</td><td>3</td></tr><tr><td>Dams</td><td></td><td></td><td></td><td></td></tr><tr><td>No. Pregnant Dams</td><td>20</td><td>20</td><td>18</td><td>19</td></tr><tr><td>No. Found Dead</td><td>1</td><td>3</td><td>5</td><td>3</td></tr><tr><td>Unscheduled Euthanasia</td><td>2</td><td></td><td>3</td><td>1</td></tr><tr><td>Aborted</td><td>1</td><td>2</td><td>1</td><td>2</td></tr><tr><td>Litters</td><td></td><td></td><td></td><td></td></tr><tr><td>No. Litters Evaluated</td><td>15</td><td>15</td><td>7</td><td>12</td></tr><tr><td>No. of Live Fetuses</td><td>8.6</td><td>8.4</td><td>8.1</td><td>8.5</td></tr><tr><td>Mean Fetal Body Weight</td><td>42.4</td><td>40.3</td><td>40.1</td><td>37.8</td></tr><tr><td>Fetal Sex Ratio</td><td></td><td></td><td></td><td></td></tr><tr><td></td><td>(% live males)</td><td>56.6</td><td>50.2</td><td>51.6</td><td>55.0</td></tr></table>	Daily Dose (mg/kg)	0	0.3	1	3	Dams					No. Pregnant Dams	20	20	18	19	No. Found Dead	1	3	5	3	Unscheduled Euthanasia	2		3	1	Aborted	1	2	1	2	Litters					No. Litters Evaluated	15	15	7	12	No. of Live Fetuses	8.6	8.4	8.1	8.5	Mean Fetal Body Weight	42.4	40.3	40.1	37.8	Fetal Sex Ratio						(% live males)	56.6	50.2	51.6	55.0
Daily Dose (mg/kg)	0	0.3	1	3																																																										
Dams																																																														
No. Pregnant Dams	20	20	18	19																																																										
No. Found Dead	1	3	5	3																																																										
Unscheduled Euthanasia	2		3	1																																																										
Aborted	1	2	1	2																																																										
Litters																																																														
No. Litters Evaluated	15	15	7	12																																																										
No. of Live Fetuses	8.6	8.4	8.1	8.5																																																										
Mean Fetal Body Weight	42.4	40.3	40.1	37.8																																																										
Fetal Sex Ratio																																																														
	(% live males)	56.6	50.2	51.6	55.0																																																									
Toxicokinetics (AUC0-24 values for infigratinib and metabolites)	Average of AUC (hr.ng/mL) Total 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 0.3 1 3 0.3 1 3 0.3 1 3 0.3 1 3 0.3 1 3 0.3 1 3 0.3 1 3 7 19 7 19 7 19 7 19 7 19 7 19 7 19 7 19 7 19 7 19 7 19 BGJ398 BHS697 BQR917 CQM157 Parent/Metabolite GD Dose (mg/kg) + −																																																													

LD: low dose; MD: mid dose; HD: high dose

LD: low dose; MD: mid dose; HD: high dose

5.5.5. Other Toxicology Studies

The Applicant's Position:

Local Tolerance studies: The irritant and/or corrosive effects of infigratinib (phosphate salt) when applied as a single dermal application was assessed on New Zealand White rabbits. No skin irritation was observed in any of the animals. The irritant and/or corrosive effects of infigratinib (phosphate salt) when administered as a single ocular administration was assessed on New Zealand White rabbits. According to the Kay and Calandra Evaluation Criteria,

infigratinib was considered to be a mild irritant to ocular tissues in rabbits. According to the EEC Ocular Evaluation Criteria, infigratinib was classified as a non-irritant in all 3 test eyes.

Mechanistic studies: A 2-week repeat-dose non-GLP rat toxicity study with an 8-week recovery period was conducted to further assess ectopic tissue mineralization in older (10-12 months) male rats. The administration of infigratinib to 10-12 month old rats for 2 weeks was well tolerated and no mineralization of any tissue was observed at ≤ 15 mg/kg/day. A 2-week repeat dose non-GLP rat toxicity study was conducted to further assess the time course and reversibility of ectopic tissue mineralization observed previously in rats after repeat administration of infigratinib. The oral administration of infigratinib to male rats for 2 weeks at 10 or 20 mg/kg/day was not tolerated; at 20 mg/kg/day this led to early termination after 6 days of dosing. A 4-week non-GLP oral gavage exploratory study in Brown-Norway and Wistar Han rats investigated the mechanism(s) and/or potential strain specificity of the corneal findings with infigratinib (phosphate salt) and BJA855 (a pharmacologically inactive analogue of infigratinib) by assessing ophthalmology, histopathology, and immunohistochemistry endpoints. Administration of infigratinib generally caused clinical chemistry effects on calcium/phosphorus homeostasis, and ophthalmic and microscopic findings in the eye and associated tissues. Corneal opacity and eye-related microscopic findings were not rat strain specific and appeared to be related to the pharmacologic mechanism (inhibition of FGFR1-3) of infigratinib.

Phototoxicity studies: The potential of infigratinib to produce phototoxic effects was assayed in Balb/c 3T3 cells. Infigratinib was not phototoxic in an in vitro 3T3 assay.

Metabolite studies: Infigratinib and its major metabolites were not considered to be mutagenic or clastogenic in a series of genetic toxicity tests.

The FDA's Assessment:

The Applicant conducted a mini-Ames assay for CQM157 and in silico bacterial mutagenicity assessments for CQM157 and BHS697 that were negative.

X

X

Dubravka Kufrin
Primary Reviewer

Matthew Thompson
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Infigratinib is a kinase inhibitor of fibroblast growth factor receptors 1-3 (FGFR1-3). The Applicant is seeking approval of infigratinib for 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. The Applicant's proposed dosing regimen is 125 mg administered orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles on an empty stomach (fasted 1 hour before or 2 hours after a meal).

The proposed dosage which was selected in the dose finding study based on a maximum tolerated dose (MTD) approach, has not been adequately justified. Specifically, 69% of patients required dose interruptions and 60% of patients required dose reductions for the management of toxicities. A total of 15% of patients experienced dose discontinuation due to TEAEs. In addition, there was a lack of favorable exposure-response relationships for efficacy and safety.

The clinical pharmacology key review questions focused on the appropriateness of the proposed dosing regimen for the general patient population, dose recommendations for patients with renal impairment and hepatic impairment, and determining the drug-drug interaction potential for infigratinib as a substrate and as a perpetrator.

The review also explored the association of FGFR2 fusions or other rearrangements and treatment response in patients included in the primary efficacy population. In addition to dosage-related issues, it is possible that genomic modifiers of response are contributing to the observed response rates (ORR 23.1%). Of note, kinase domain mutations associated with resistance to FGFR2 inhibitors were identified in the post-progression biopsies of 2 patients.

Post marketing requirements and commitments were agreed for the conduct of studies addressing review issues.

6.1.1. Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 214622 and recommends approval. The key review issues with specific recommendations and/or comments are summarized below. Post-marketing requirements and commitments are detailed in Table 7.

Review Issues	Recommendations and Comments
---------------	------------------------------

Pivotal evidence of effectiveness	An open-label, single arm trial (Study CBGJ398X2204 Phase 2 Cohort 1) of infigratinib in patients advanced or metastatic cholangiocarcinoma with FGFR genetic alterations.
General Dosing instructions	The Applicant's proposed recommended dosage of infigratinib is 125 mg administered once daily (QD) orally without food. This dosage needs a further optimization from a clinical pharmacology perspective: • 125 mg QD is the MTD determined in dose finding studies with 1 DLT out of 8 patients receiving this dose level. • Significant dosage modifications were needed to manage toxicities in patients receiving the proposed dosage in study CBGJ398X2204, including 69% dose interruption and 60% dose reduction. • Exposure-response analysis for safety suggests a positive relationship for hyperphosphatemia and eye disorder. The hyperphosphatemia rate was confounded by the use of prophylactic phosphate binders and treatment with phosphate binders with serum phosphate ≥ 5.5 mg/dL in 80% of patients enrolled in study CBGJ398X2204. • Exposure-response analysis for efficacy suggests a negative to flat relationship for best overall response (BOR).
Dosing in patient subgroups (intrinsic factors)	• The recommended dosage for use in patients with severe hepatic impairment (total bilirubin $> 3 \times$ upper limit of normal [ULN] with any AST) has not been established. Labeling will include instructions to reduce infigratinib dose to 100 mg in patients with mild hepatic impairment (total bilirubin > 1 to $1.5 \times$ ULN or AST $>$ ULN) and to reduce infigratinib dose to 75 mg in patients with moderate hepatic impairment (total bilirubin > 1.5 to $3 \times$ ULN with any AST). • The recommended dosage for use in patients with severe renal impairment (creatinine clearance [CLcr] < 30 mL/min calculated by Cockcroft-Gault) has not been established. Labeling will include instructions to reduce infigratinib dose to 100 mg in patients with mild or moderate renal impairment (CLcr 30 to 89 mL/min). • Based on available data, no dose adjustment is recommended based on age, race, or sex.
Drug-drug interactions	Labeling will include instructions to: • Avoid concomitant use of infigratinib with strong or moderate CYP3A inhibitors or inducers.

	Avoid concomitant use of infigratinib with acid reducing agents. If use of a H2 antagonist or locally acting acid is required, modify administration time.
QTc Assessment	At the recommended dosing regimen, infigratinib does not result in a large mean increase (i.e. >20 msec) in the QTc interval. The QT effect of infigratinib at higher exposures associated with CYP3A4 inhibition has not been studied.
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the label.
Bridge between the to-be-marketed and clinical trial formulations	A total of 5 formulations, i.e., Clinical Service Form (CSF), Final Marketed Image (FMI) I-IV were evaluated in the clinical development program of infigratinib. In this NDA, FMI-I, FMI-III, and the to-be-marketed formulation, i.e., FMI-IV, were used in the CBGJ398X2204 trial. The bridging between the formulations and the to-be-marketed formulation was demonstrated based on the totality of in vitro, PK comparison, safety, and efficacy data.

6.1.2. Post-Marketing Requirements and Commitments

The rationale and descriptions of post-marketing requirements (PMR) and commitments (PMC) are summarized in the table below. The PMC and PMRs are issued to further optimize the dosage and to address the drug interaction potential for infigratinib as a substrate and as an inhibitor. In addition, a PMC was requested to evaluate potential mechanisms of resistance to infigratinib.

Table 7. Summary of Clinical Pharmacology Post-Marketing Requirements and Commitments

Post-Marketing Requirement-1	
PMR Rationale	At the Applicant recommended dosage of 125 mg once daily (QD) 21 days on/7 days off used in study CBGJ398X2204, dosage modification due to adverse events (AEs) were observed in 79% of patients, including 64% for dose interruption and 60% for dose reduction, leading to an actual median relative dose intensity of approximately 100 mg. A flat to negative exposure-efficacy relationship for best overall response (BOR) and a positive exposure-safety relationship for hyperphosphatemia and eye disorder were identified in exploratory analyses. Phosphate binders were used in a total of 80% (87/108) patients in the study. In addition, the most common adverse reactions leading to dose interruption and/or

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	reduction was hyperphosphatemia (78%), indicating a potential maximum receptor saturation at the recommended dosage. Based on the above, further dose optimization is needed from a safety perspective.
PMR Description	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 regimens of infigratinib. Characterize all serious adverse events including hyperphosphatemia and eye disorders, dose reductions, interruptions, and discontinuations due to 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.
Post-Marketing Requirement-2	
PMR Rationale	Infigratinib is primarily metabolized by CYP3A4 in vitro. In the single dose studies in healthy subjects, infigratinib drug exposure increased by 7-fold when coadministered with a strong CYP3A inhibitor (itraconazole). The risk of concomitant use of moderate CYP3A inhibitors to increase infigratinib plasma exposure, leading to increased adverse reactions, cannot be ruled out.
PMR Description	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.”
Post-Marketing Requirement-3	
PMR Rationale	Infigratinib is a P-gp substrate in vitro. The risk of P-gp inhibitors increasing infigratinib plasma exposure leading to increased adverse reactions, has not been ruled out.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

PMR Description	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. ”
Post-Marketing Requirement-4	
PMR Rationale	Infigratinib is a BCRP inhibitor and substrate in vitro. BCRP may potentially be responsible in part for the infigratinib plasma exposure accumulation ratio of 8-fold for C_{max} and 5-fold for AUC at steady state following a dosage of 125 mg QD in patients. The risk of concomitant use of BCRP inhibitors to increase infigratinib plasma exposure, leading to increased adverse reactions, and the 8-fold drug exposure increase at steady state, can not be ruled out.
PMR Description	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. ”
Post-Marketing Requirement-5	
PMR Rationale	Infigratinib is a BCRP inhibitor and substrate in vitro. BCRP is potentially responsible for the infigratinib plasma exposure accumulation ratio of 8-fold for C_{max} and 5-fold for AUC at steady state following a dosage of 125 mg QD in patients. In addition, the effect of infigratinib on increasing plasma exposures of BCRP substrates cannot be ruled out.
PMR Description	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. ”
Post-Marketing Requirement-6	

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

PMR Rationale	Infigratinib is a MATE1 inhibitor in vitro. The in vitro inhibition potential of its major metabolites (BHS697, CQM157, BQR917) on transporters MATE1/2 and OCT1/2, has not been assessed. In clinical studies with infigratinib, in patients with solid tumors, 26 patients were identified who were concomitantly administered metformin (MATE1/2 and OCT1/2 substrate), 3 of these patients developed hypoglycemia. The risk of infigratinib and its major metabolites on increasing plasma exposures of MATE and OCT substrates, leading to increased adverse reactions, cannot be ruled out.
PMR Description	Conduct in vitro study to evaluate the drug-interaction potential of the major metabolites, i.e., 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. "
Post-Marketing Commitment-1	
PMC Rationale	Infigratinib is primarily metabolized by CYP3A4 in vitro. In the single dose study in healthy subjects, infigratinib drug exposure decreased by 58% when coadministered with a strong CYP3A inducer (rifampin). The risk of concomitant use of moderate CYP3A inducers to decrease infigratinib plasma exposure, leading to reduced efficacy, cannot be ruled out.
PMC Description	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. "
Post-Marketing Commitment-2	
PMC Rationale	Emergence of secondary FGFR2 mutations have been associated with resistance to FGFR inhibitors in patients with cholangiocarcinoma. During the CBGJ398X2204 study, separate mutations in the FGFR2 kinase domain, p.N549K and p.V564L, were identified in post-progression biopsy tissue of two patients out of four with available data. These two mutations were previously identified as resistance mutations to FGFR2 inhibitors. Molecular characterization of tumors (tissue and/or cell free DNA) at baseline, on-treatment and at the time of progression may allow for uncovering primary and acquired resistance mechanisms to infigratinib, help inform therapy combinations and optimize patient selection.

PMC Description	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 the ongoing clinical trial QBGJ398-301 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.
-----------------	--

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Refer to [Table 16](#) in Section [6.3.1](#) for a summary of clinical pharmacology characteristics for infigratinib.

The Applicant's Position:

A comprehensive clinical pharmacology program was conducted for infigratinib and its active metabolites in Phase 1 and Phase 2 studies to support the use of infigratinib for the treatment of cholangiocarcinoma. Phase 1 clinical studies evaluated single- and multiple-dose escalations in oncology patients.

Single dose studies of infigratinib in healthy subjects assessed the mass balance of infigratinib, the potential for other drugs to affect infigratinib, and the food effects. Multiple doses of infigratinib were investigated in healthy subjects for the potential to affect the PK of a sensitive CYP3A4 substrate. The impact of mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment was assessed in non-oncology subjects and in healthy subjects matched by demographics.

Population PK analyses evaluated intrinsic and extrinsic factors affecting the PK of infigratinib and its metabolites in patients with cholangiocarcinoma, and potential relationships were evaluated between infigratinib and its active metabolites' exposure and efficacy and safety outcomes in the exposure-response (E-R) analyses. Finally, PK/PD analysis was conducted to assess the relationship between the exposure and QT/QTc to exclude clinically relevant effects on QT by infigratinib or its major metabolites.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical pharmacology program supports the use of infigratinib for the treatment of cholangiocarcinoma. However, the current submission provided insufficient data to support the Applicant's proposed recommended

dosage of 125 mg QD 21 days on/7 days off as an optimal dosage. As a result, FDA issued a PMR to further evaluate alternative dosage(s) in patients with cholangiocarcinoma in ongoing or planned trials. See Section 6.2.2.1 below for the detailed reviewer's assessment of the recommended dosage.

In addition, the current submission did not provide sufficient data to evaluate the drug interaction potential for infigratinib as a substrate or inhibitor. As a result, FDA issued five PMRs and one PMC to evaluate the effects of moderate CYP3A4 inhibitors, moderate CYP3A4 inducers, P-gp inhibitors, BCRP inhibitors on infigratinib exposure, respectively and the effect of infigratinib on exposures of BCRP substrates and MATE1 substrates, respectively. See Section 6.3.2.4 below for the detailed reviewer assessment of the drug-drug interaction potential.

The assessment of dosage recommendations for patients with renal and hepatic impairment was based on PK matching to the patients with normal organ function at steady state from Study 2204. See Section 6.2.2.2 below for the detailed reviewer assessment of organ impairment.

The clinical pharmacology program for the current NDA includes the following assessments supported by a total of seventeen clinical trials with twelve trials in healthy subjects and five trials in patients with cancer:

- Dose selection/Dose Confirmation

- o CBGJ398X2101: dose escalation study of infigratinib in adult patients with advanced solid malignancies.
- o CBGJ398X1101: dose finding study of infigratinib in Asian patients with solid tumors with FGFR alterations.
- o CBGJ398X2102: dose escalation study of infigratinib in combination with a PI3K inhibitor in adult patients with select advanced solid tumors.
- o CBGJ398X2201: a Phase 2 study of infigratinib in patients with recurrent resectable or unresectable glioblastoma.
- o CBGJ398X2204: a Phase 2, single arm study of infigratinib with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy. (Registrational trial, Study CBGJ398X2204)

- Dedicated Hepatic Impairment

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

- o QBGJ398-107: single-dose, parallel-group study to evaluate the PK and safety of infigratinib in subjects with chronic hepatic impairment.
- Dedicated Renal Impairment
 - o QBGJ398-110: single-dose, parallel-group study to evaluate the PK and safety of infigratinib in subjects with renal impairment.
- Drug Interaction
 - o QBGJ398-102: fixed-sequence study to evaluate the effect of multiple doses of rifampin on the PK of a single dose of infigratinib in healthy subjects.
 - o QBGJ398-103: fixed-sequence, 2-period study to evaluate the effect of multiple doses of itraconazole on the PK of a single dose of infigratinib in healthy subjects.
 - o QBGJ398-104: fixed-sequence, 2-period study to evaluate the effect of multiple doses of lansoprazole on the PK of a single dose of infigratinib in healthy subjects.
 - o QBGJ398-106: fixed-sequence, 2-period study to evaluate the effect of multiple doses of infigratinib on the PK of a single dose of midazolam in healthy subjects.
- Food Effect, Relative BA/BE
 - o CBGJ398X2103: randomized crossover study to evaluate the food effect of infigratinib FMI-I formulation and the relative BA of infigratinib FMI-I and CSF formulations in healthy subjects.
 - o CBGJ398A2104: randomized, two-period crossover study to evaluate the relative BA of infigratinib FMI-II and CSF formulations in healthy subjects.
 - o CBGJ398X2105: randomized, crossover study to evaluate the food effect and dose effect on the relative BA of infigratinib FMI-II and CSF formulations in healthy subjects.
 - o CBGJ398X2106: randomized crossover study to evaluate the food effect of infigratinib FMI-III formulation and the relative BA of infigratinib FMI-III and CSF formulations in healthy subjects.
- Mass Balance, PK
 - o QBGJ398-101: single-dose study to evaluate the excretion and mass balance, PK, and metabolism of [¹⁴C]infigratinib in healthy male subjects.

- o QBGJ398-109: one-period, single-dose study to evaluate the PK of infigratinib FMI-IV formulation in healthy subjects.

The to-be-marketed formulation for infigratinib is FMI-IV. Five infigratinib capsule formulations (CSF, FMI-I, FMI-II, FMI-III, and FMI-IV) were used in the clinical pharmacology studies. Dose finding and dose confirmation assessments were conducted with the CSF and FMI-I formulations, while drug interaction and dedicated renal and hepatic impairment assessments were conducted with FMI-III. In Study CBGJ398X2204, as of the cutoff date August 19, 2020, patients mainly received the FMI-I (51/108) and FMI-III (48/108) infigratinib formulations, and a relatively small proportion of patients received the FMI-IV (9/108) infigratinib formulation. Intensive PK sampling was available in 20 patients taking FMI-III, while only sparse PK samples were collected in the rest of the patients enrolled in this study. (Appendix 19.4.2).

FDA concludes that adequate bridging has been established across the CSF, FMI-I, FMI-III, and FMI-IV formulations, as supported by the totality of safety, efficacy, PK, and in vitro dissolution comparability data. PK comparability of these four formulations was further established based on the pooled PK analysis across single dose studies in healthy volunteers.

Concentrations of infigratinib and its active metabolites (BHS697, CQM157) in human plasma samples were analyzed via liquid chromatography coupled with tandem mass spectrometric detection (LC-MS/MS). All LC-MS/MS assays were validated or partially validated according to applicable guidance (Bioanalytical Method Validation, FDA Guidance for Industry; Guideline on Bioanalytical Method Validation, EMA) and fulfilled requirements with respect to linearity, selectivity, accuracy, and precision (Refer to section 19.4 for more details on bioanalytical methods).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

Selection of the recommended dose was based on the first-in-human dose escalation/dose expansion study CBGJ398X2101. This study evaluated the safety and maximum tolerated dose (MTD), efficacy, and PK of infigratinib increasing oral doses of 5 mg to 150 mg QD, 50 mg BID, and 125 mg QD 3 weeks on/1 week off. In this study the MTD was declared at 125 mg QD (continuous dosing) and the recommended Phase 2 dose (RP2D) was 125 mg QD 3 weeks on/1 week off. The safety and efficacy of infigratinib 125 mg QD 3 weeks on/1 week off was further evaluated in the Phase 2 study CBGJ398X2204 in second line cholangiocarcinoma patients with FGFR genetic alterations. Exposure-Response analyses for efficacy and safety were conducted for Study CBGJ398X2204. Food effect studies showed that infigratinib administration with food increased the exposure by 1.7 to 2.2-fold in terms of AUC_{inf} ; therefore, infigratinib was administered 1 hour before or 2 hours after a meal in patient trials.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

No exposure measures were statistically significant predictors of either OR or PFS. This lack of a significant E-R relationship may be due to the relatively small sample size of patients included in these analyses. Statistically significant E-R relationships were identified for hyperphosphatemia and eye disorders (excluding central serous retinopathy/retinal pigment epithelial detachment [CSR/RPED]). Higher infigratinib exposure resulted in higher probability of hyperphosphatemia and eye disorders (excluding CSR/RPED). Phosphate binder coadministration was found to be significantly predictive of the probability of hyperphosphatemia. No additional covariates were found to be significant.

Stochastic simulations to predict the probability of hyperphosphatemia or eye disorders (excluding CSR/RPED) when administering 50, 75, 100, and 125 mg 3 weeks on/1 week off showed a minimal change in the probability of these events.

The Applicant's Position:

The recommended dose of infigratinib is 125 mg (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. Treatment is continued until disease progression or unacceptable toxicity. Capsules should be taken on an empty stomach at least 1 hour before or 2 hours after a meal, at approximately the same time each day. Starting with this dose allows patients to rapidly achieve an efficacious dose, particularly important in this refractory population with visceral disease, for which appropriate dose modifications can then be made based on on-target AEs and changes in laboratory values such as hyperphosphatemia.

The FDA's Assessment:

FDA does not agree with the Applicant that the proposed recommended dosage for general population is adequately supported by the data or analyses included in the NDA submission, based on the following:

1. The proposed 125 mg QD dosage is the MTD as determined in the dose finding CBGJ398X2101. At the 125 mg continuous daily dosage used in this study, 1/8 patients experienced 1 DLT (hyperphosphatemia > 14 days) on Day 8 following initiation of treatment. Based on this identified MTD, the dosing frequency was subsequently reduced from 125 mg once daily continuously, to 125 mg once daily for 21 days in 28-day cycle. However, based on the pharmacokinetics of infigratinib, this change in regimen does not change the steady state exposure. The same maximum steady state drug exposure is reached on Day 15 following both the continuous and the 21 days-on dosing regimens.
2. In Study CBGJ398X2204, dose modification due to adverse events (AEs) was observed in a significant proportion of patients at the proposed recommended dosage, including 69% for dose interruption (Table 44) and 60% for dose reduction (Table 45). The median relative dose intensity was 78%, which is approximately equivalent to the 100

mg dose level.

3. The majority of patients had dose interruptions or dose reductions before achieving a response (Figure 4). The earliest evaluation for response occurred after 2 treatment cycles (week 8) with 16% of patients achieving a response. About half of the patients in Cycle 1 experienced dose interruptions, and over 1/3 of the patients had a dose reduction in Cycle 2. The percentages of patients receiving infigratinib at lowest daily dose levels of 125 mg/100 mg/75 mg/50 mg was 34.3%/25.9%/31.5%/7.4%. Given few assessments of response are available before these dose modifications, it is unknown if responses occurred before dose reductions, or if a high starting dose is needed for a response in subsequent treatment cycles.
4. Assessment of exposure-efficacy relationship showed a flat to negative trend when evaluating exposures achieved at the following a starting dose of 125 mg. The 125 mg starting dose was already reduced to a range between 50 mg and 100 mg in the majority of patients at the occurrence of best overall response (BOR) (Table 8), suggesting that an alternative lower dosage regimen may still provide comparable efficacy. (Figure 5)
5. A positive exposure-response relationship was reported for hyperphosphatemia (Figure 6) and eye disorder (excluding CSR/RPED, Figure 7). Based on E-R model simulations conducted, the Applicant concluded that there is a minimal change in the probability of hyperphosphatemia over the dosage range from 50 mg to 125 mg. This conclusion is not justified due to confounding factor, i.e., early and prophylactic use of phosphate binder during treatment with infigratinib. In addition, the Applicant used the AE dataset to assess the incidence of hyperphosphatemia reported as an adverse event instead of lab safety dataset, which may result in underestimation of the incidence of hyperphosphatemia. Of note, in Study CBGJ398X2204, a total of 48% (52/108) patients were administered a phosphate binder prophylactically at baseline and another 32% (35/108) patients were administered a phosphate binder during the study treatment period. Given these significant issues, the effect of exposure on the probability of hyperphosphatemia is likely underestimated by the Applicant.
6. The most common TEAE leading to dose interruption and dose reduction was hyperphosphatemia (78%), indicating a potential maximum receptor saturation following the proposed dosage.

Based on review of the available data, the recommended dosage is not adequately justified from a clinical pharmacology perspective, and the further dosage optimization is needed from a safety and efficacy perspective. The Applicant will need to evaluate one or more alternative dosages to find a dosage in which efficacy is maintained with an improved safety profile.

Of note, the $AUC_{activity}$ used throughout the review section, refers to the potency adjusted AUC

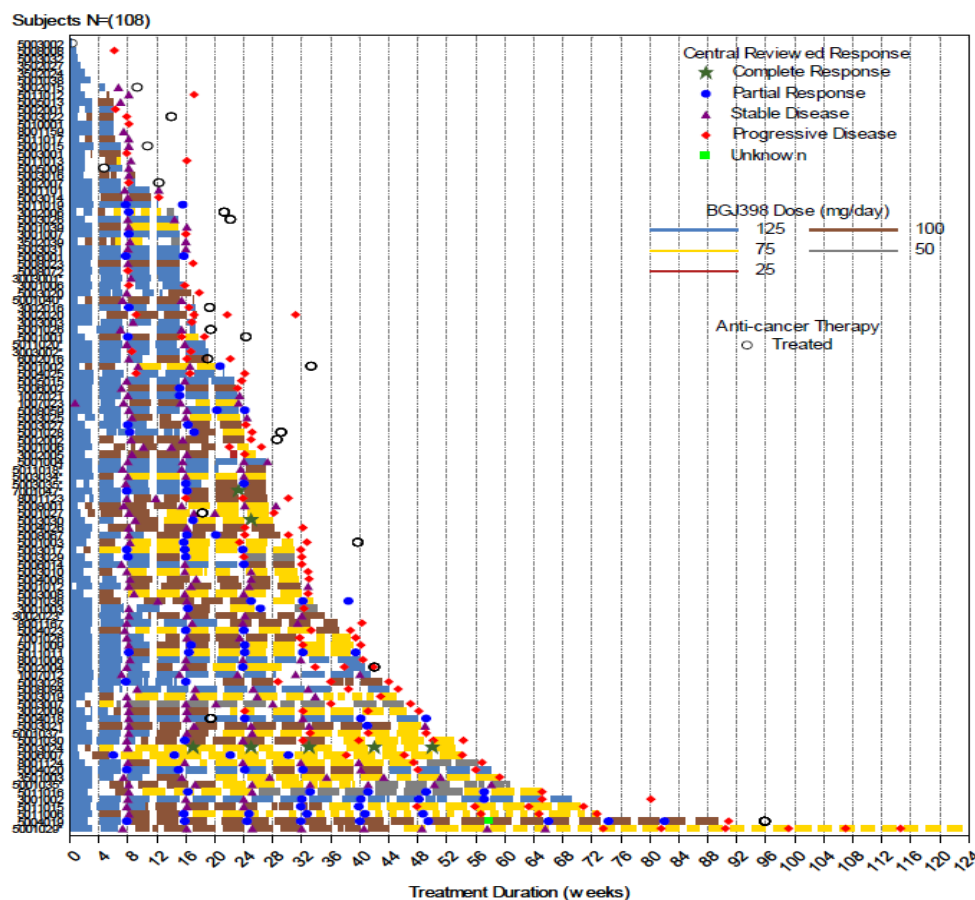
with consideration of the active metabolites BHS697 and CQM157, i.e.,

$$AUC_{activity} = AUC_{infigratinib} + \left(\frac{K_{d,infigratinib}}{K_{d,BHS697}} \right) * AUC_{BHS697} + \left(\frac{K_{d,infigratinib}}{K_{d,CQM157}} \right) * AUC_{CQM157}$$

where Kd represents the dissociation constant of each moiety to FGFR1-4.

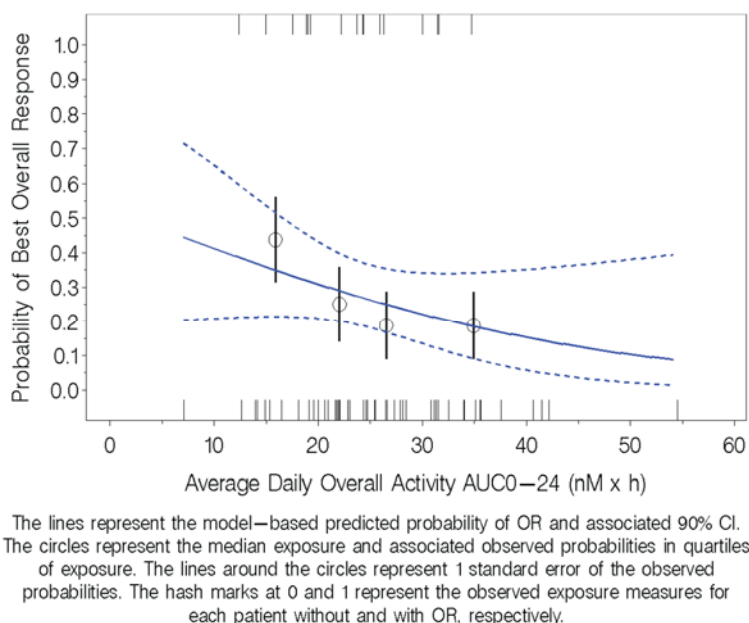
FDA agrees with the Applicant's assessment that infigratinib should be taken on an empty stomach at least 1 hour before or 2 hours after food.

Figure 4. Tumor Response with Treatment Exposure.



Source: EDR 5.3.5.2 Study cbgj398x2204 report Figure 14.2.12.1.

Figure 5. Model predicted (90%) probability of best overall response versus potent adjusted AUC_{activity} (nM*h) for infigratinib, BHS697, and CQM157 with observed data overlaid.



*Range of AUC quartiles: Q1 [7.07279-19.4003], Q2 [19.4003-24.3458], Q3 [24.3458-31.2448], Q4 [31.2448-54.5328].

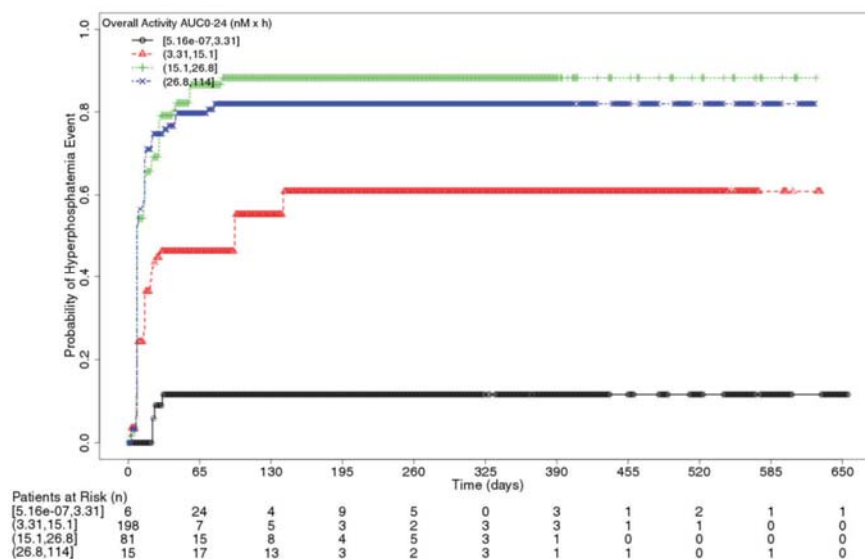
Source: EDR 5.3.4.2 Study QED-PMX-002 report Figure 5 and Table 12.

Table 8. Subject number stratified by last dose at the occurrence of BOR.

Endpoint		Last dose at the occurrence of BOR (mg)				
		50 (N=7)	75 (N=34)	100 (N=28)	125 (N=33)	Overall (N=102)
Best overall response, n (%)	No	5 (71.4%)	23 (67.6%)	21 (75.0%)	28 (84.8%)	77 (75.5%)
	Yes	2 (28.6%)	11 (32.4%)	7 (25.0%)	5 (15.2%)	25 (24.5%)

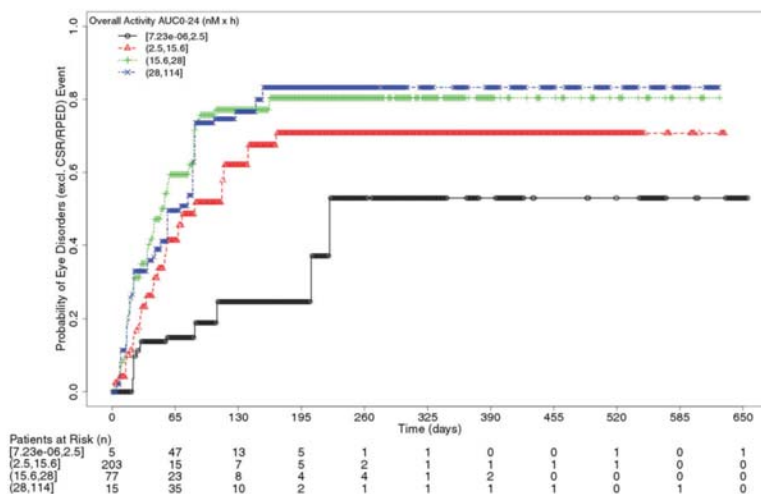
Source: Reviewer's summary based on adrs.xpt and s2204or.xpt from Study 2204.

Figure 6. Kaplan-Meier plot of probability of hyperphosphatemia versus time, by quartile of potency adjusted AUC_{activity} (nM*h).



Source: EDR 5.3.4.2 Study QED-PMX-002 report Figure 10.

Figure 7. Kaplan-Meier plot of probability of eye disorders (excluding CSR/RPED) versus time, by quartile of potency adjusted AUC_{activity} (nM*h).



Source: EDR 5.3.4.2 Study QED-PMX-002 report Figure 20.

6.2.2.2. Therapeutic Individualization

Data:

Not Applicable.

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors, including age, weight, sex, and race, as no clinically relevant differences were identified in the population PK model. No therapeutic individualization is needed for patients with mild hepatic or renal impairment based on the <2-fold change in exposure in subjects with mild hepatic impairment and the population PK model results comparing cholangiocarcinoma patients with normal renal function vs patients with mild renal impairment. Clinically significant exposure change (>2-fold) of infigratinib was observed in subjects with moderate hepatic impairment. Similarly, in the population PK model that assessed the exposure of infigratinib in cholangiocarcinoma patients by NCI liver function criteria, a trend towards increased exposure with moderate liver function was observed. Therefore, a starting dose of infigratinib 75 mg QD 3 weeks on/1 week off is recommended for patients with moderate hepatic impairment.

The FDA's Assessment:

Renal impairment:

(b) (4)

Although the mass balance study demonstrated minimal renal elimination of unchanged infigratinib, dose reduction is necessary for patients with mild and moderate renal impairment based on the Applicant's updates with results from a dedicated renal impairment study, as well as the safety and PK assessments from the CBGJ398X2204 trial:

1. In the dedicated renal impairment study in 110 adult subjects, the geometric mean AUC_{inf} increased by 58% in subjects with moderate renal impairment taking a single dose infigratinib 125 mg, compared to subjects with normal function. No studies were conducted in subjects with mild renal impairment. (Table 9).
2. In Study CBGJ398X2204, the rates of TEAE-related dose interruption/reduction increased in patients with normal (76.1%), mild (82.8%), or moderate (100%) renal impairment. The overall trend of serious treatment-related TEAE rate and TEAE leading to treatment discontinuation also increased with the severity of renal impairment. (Table 10).
3. In Study CBGJ398X2204, a total of 36.6% (26/71) patients with normal renal function received infigratinib at 125 mg as the lowest daily dose level during the study, while a total of 42.9% (3/7) patients with moderate renal impairment received infigratinib at 100 mg as the lowest daily dose level. The specific percentages of patients receiving infigratinib at lowest daily dose levels of 125 mg/100 mg/75 mg/50 mg were:

- o 36.6%/25.4%/32.4%/4.2% for N=71 patients with normal renal function,
- o 31.0%/24.1%/31.0%/13.8% for N=29 patients with mild renal impairment, and
- o 28.6%/42.9%/28.6%/0 for N=7 patients with moderate renal impairment.

4. In Study CBGJ398X2204 at steady state, the population PK estimated relative potency adjusted AUC ($AUC_{activity}$) of infigratinib plus its active metabolites (BHS697, CQM157) in plasma increased by 32% in patients with mild renal impairment and by 37% in patients with moderate renal impairment respectively, relative to patients with normal renal function (Table 11).
5. The MTD was selected as the starting dose of infigratinib for the general patient population, and elevated infigratinib exposure would cause additional safety concerns if no dose reduction is implemented for patients with renal impairment.

Based on the above, FDA recommends a starting dose of 100 mg QD for 21 days in 28-day cycle for patients with mild and moderate renal impairment (Creatinine clearance [CLcr] 30 to 90 mL/min estimated by Cockcroft-Gault equation). This dosage recommendation is based on the following considerations:

- a. For patients with mild renal impairment, the starting dose of 100 mg QD was based on matching the steady state $AUC_{activity}$ by using population PK simulation in Study CBGJ398X2204. Specifically 20 patients with renal impairment, i.e., CLcr at 60 to < 90 mL/min were compared to 52 patients with normal renal function, i.e., CLcr $\geq$ 90 mL/min. (Table 11) This PK simulation result has been verified by the reviewer's analysis (Appendix 19.4.2.4).
- b. For patients with moderate renal impairment, a population PK simulation was conducted to match the steady state $AUC_{activity}$ in the 7 patients with moderate renal impairment (CLcr at 45 to < 60 mL/min) to the 52 patients with normal renal function in Study CBGJ398X2204. The PK simulation supports a starting dose of 100 mg QD in patients with moderate renal impairment and has been verified by the reviewer's analysis (Appendix 19.4.2.4). A total of 5 out of the 7 patients with moderate renal impairment required a permanent dose reduction from the 125 mg dose level, further supporting the need of starting dose reduction at this subgroup of patients. Further dose reduction, based on individual tolerability and serum phosphate, may be implemented based on recommendations in Section 2 of the proposed package insert.

Based on the above, FDA recommends a starting dose of 100 mg QD for 21 days in 28-day cycle in patients with mild and moderate renal impairment.

Table 9. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with moderate renal impairment (Test) to healthy subjects with normal renal function (reference).

Analyte	PK parameter	GeoMean Test	GeoMean Ref	Ratio (%) (Test/Ref)	90% CI
Infigratinib	C _{max} (ng/mL)	32.1	32.5	98.8	(48.8, 228.2)
	AUC _{last} (h*ng/mL)	392	291	134.9	(62.8, 289.8)
	AUC _{inf} (h*ng/mL)	512	325	157.8	(74.2, 335.4)
CQM157	C _{max} (ng/mL)	31.9	36.2	88.2	(50.7, 153.5)
	AUC _{last} (h*ng/mL)	1050	987	106.8	(67.6, 168.6)
	AUC _{inf} (h*ng/mL)	1480	1080	136.8	(80.0, 234.0)
BHS697	C _{max} (ng/mL)	8.66	5.88	147.2	(64.6, 335.7)
	AUC _{last} (h*ng/mL)	161	95.0	169.0	(88.1, 324.0)
	AUC _{inf} (h*ng/mL)	246	124	199.0	(91.4, 433.4)

Source: EDR 5.3.3.3 Study QBGI398-110 report Table 17.

Table 10. TEAEs leading to dose modification stratified by renal function categories.

Dose Modification	Normal (n=71) CLcr ≥ 90 mL/min	Mild RI (n=29) CLcr 60 to < 90 mL/min	Moderate RI (n=7) CLcr 45 to < 60 mL/min
TEAEs leading to dose interruption	63.4% (45/71)	62.1% (18/29)	85.7% (6/7)
TEAEs leading to dose reduction	54.9% (39/71)	69.0% (20/29)	57.1% (4/7)
TEAEs leading to dose discontinuation	11.3% (8/71)	13.8% (4/29)	42.9% (3/7)

Source: EDR 1.11.3 Response to FDA RFI-ClinPharm -23 Dec 2020.

Table 11. Simulated potency adjusted AUC_{activity} (μM*h) of infigratinib and BHS697, CQM157 for each renal impairment category in Study CBGI398X2204 at 125 mg, 100 mg, and 75 mg.

NCI criteria	N	AUC _{activity,ss} Geometric Mean and 90% CI		
		125 mg	100 mg	75 mg
Normal renal function CLcr ≥ 90 mL/min	52	41.4 (22.2, 70.6)	33.1 (17.8, 56.5)	24.8 (13.4, 42.4)
Mild renal impairment CLcr 60 to < 90 mL/min	20	54.7 (34.0, 103.5)	43.8 (27.2, 82.8)	32.8 (20.4, 62.1)
Moderate renal impairment CLcr 45 to < 60 mL/min	7	56.9 (38.5, 73.8)	45.5 (30.8, 59.0)	34.2 (23.1, 44.3)

Source: EDR 1.11.3 Response to FDA RFI-ClinPharm -23 Dec 2020.

Hepatic Impairment:

(b) (4)

Dose reduction is necessary for patients with mild hepatic impairment based on the Applicant's updates with results from the dedicated hepatic impairment study as well as the safety and PK assessments from study CBGI398X2204.

Of note, the dedicated hepatic impairment study was conducted following Child Pugh criteria; when reclassifying patients following the NCI-OWDG criteria, the results were consistent.

1. In the dedicated hepatic impairment study 107, the geometric mean AUC_{inf} increased by 86% and 162% in subjects with mild and moderate hepatic impairment following a single dose infigratinib 125 mg, respectively compared to subjects with normal hepatic function. (Table 12, Table 13)
2. In Study CBGJ398X2204, the rates of TEAE-related dose interruption and/or reduction increased in patients with normal (60.4%/54.7%), mild (66.0%/64.0%), or moderate (75.0%/75.0%) hepatic impairment. The overall trend of serious (treatment-related) TEAE rate also increased with severity of hepatic impairment. (Table 14)
3. In Study CBGJ398X2204, a total of 37.7% (20/53) patients with normal hepatic function received infigratinib at 125 mg as the lowest daily dose level during the study, while a total of 40% (20/50) patients with mild hepatic impairment received infigratinib at 75 mg as the lowest daily dose level. The specific percentages of patients receiving infigratinib at lowest daily dose levels of 125 mg/100 mg/75 mg/50 mg were:
 - o 37.7%/26.4%/24.5%/9.4% for N=53 patients with normal hepatic function,
 - o 30.0%/24.0%/40.0%/6.0% for N=50 patients with mild hepatic impairment, and
 - o 50%/50%/0/0 for moderate hepatic impairment for N=4 patients with moderate hepatic impairment.
4. In Study CBGJ398X2204 at steady state, the population PK estimated relative potency adjusted AUC ($AUC_{activity}$) of infigratinib plus its active metabolites (BHS697, CQM157) in plasma increased by 47-62% in patients with mild hepatic impairment and by 99% in patients with moderate hepatic impairment, respectively compared to patients with normal hepatic function (Table 15).
5. The MTD was selected as the starting dose of infigratinib for the general patient population, and elevated infigratinib exposure would cause additional safety concerns if no dose reduction was implemented for patients with mild hepatic impairment.

Therefore, FDA recommends a reduced starting dose for patients with mild and moderate hepatic impairment. For patients with mild hepatic impairment, FDA recommends a starting dose of 100 mg QD for 21 days in 28-day cycle. Based on PK simulation, the steady state $AUC_{activity}$ for mild B1 and B2 was 45.6 $\mu M \cdot h$ and 50.3 $\mu M \cdot h$ following the 100 mg QD starting dose. Although the simulated AUC appears to be higher compared to patients with normal hepatic function with steady state $AUC_{activity}$ as 38.8, this 100 mg QD starting dosage for patients with mild hepatic impairment is recommended based on the following further considerations:

- a. In the 50 patients with mild hepatic impairment, although 40% patients received infigratinib with 75 mg as the lowest dosage, a total of 54% of patients received

infigratinib at a dosage of 125 mg QD and 100 mg QD throughout the study. Therefore, it is likely the 100 mg starting dose has the potential to maintain efficacy (given the uncertain flat or negative trend in the E-R for efficacy) and also appears relatively well tolerated, with a potential for additional dose reduction based on phosphate levels and individual tolerability in accordance with the proposed package insert.

- b. At a starting dose of 75 mg QD in patients with mild hepatic impairment, the simulated steady state $AUC_{activity}$ (34.2-37.7 $\mu M \cdot h$) is lower than that of patients with normal hepatic function following 125 mg QD starting dose. (Table 15) Given the inconclusive exposure-efficacy relationship, and limited patient data at the 75 mg dose level, FDA recommends a starting dose of 100 mg, in patients with mild hepatic impairment, with the potential for further dose reduction based on phosphate levels and individual tolerability as proposed in the package insert.
- c. The reviewer's analysis supports the dosage recommendation of 100 mg QD for mild hepatic impairment, where the steady state $AUC_{activity}$ has a better match to patients with normal hepatic function taking infigratinib at 125 mg QD.

Based on the above, FDA recommends a starting dose reduction to 100 mg QD for 21 days in 28-day cycle for patients with mild hepatic impairment.

FDA agrees with the Applicant's proposal of a starting dose of 75 mg QD for patients with moderate hepatic impairment. The dosage recommendations are verified based on the $AUC_{activity}$ matching at steady state using population PK simulation in Study CBGJ398X2204. Although the PK simulation is only based on 5 patients with moderate hepatic impairment and all patients received infigratinib at 125 mg QD or 100 mg QD during the study, additional support for the 75 mg starting dose is further supported by results from the dedicated study. Specifically, a single dose of 125 mg infigratinib would cause a 182% increase in AUC in subjects with moderate hepatic impairment. Therefore, a dose reduction to 100 mg will not be sufficient to reduce the safety concern associated with by the further elevated infigratinib exposure at steady state.

Table 12. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with mild hepatic impairment (Child Pugh A, Test) to healthy subjects with normal function (reference).

Analyte	PK parameter	GeoMean Test	GeoMean Ref	Ratio (%) (Test/Ref)	90% CI
Infigratinib	C_{max} (ng/mL)	83.3	46.6	178.9	(133.8, 239.2)
	AUC_t (h*ng/mL)	802	436	183.8	(124.3, 271.8)
	AUC_{inf} (h*ng/mL)	829	447	185.6	(123.5, 278.8)
CQM157	C_{max} (ng/mL)	34.4	43.1	79.8	(50.3, 126.5)
	AUC_t (h*ng/mL)	1060	1120	94.3	(57.1, 155.7)
	AUC_{inf} (h*ng/mL)	1220	1180	103.4	(61.3, 174.6)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

BHS697	C _{max} (ng/mL)	9.2	10.8	85.0	(55.0, 131.6)
	AUC _t (h*ng/mL)	150	164	91.2	(68.5, 121.6)
	AUC _{inf} (h*ng/mL)	187	208	89.7	(66.4, 121.1)

Source: EDR 5.3.3.3 Study QBGI398-107 report Table 24.

Table 13. Statistical analysis of infigratinib and CQM157, BHS697 systemic exposure, comparisons of subjects with moderate hepatic impairment (Child Pugh B, Test) to healthy subjects with normal function (reference).

Analyte	PK parameter	GeoMean Test	GeoMean Ref	Ratio (%) (Test/Ref)	90% CI
Infigratinib	C _{max} (ng/mL)	112	71.8	155.9	(101.2, 240.2)
	AUC _t (h*ng/mL)	1590	614	259.2	(154.8, 434.0)
	AUC _{inf} (h*ng/mL)	1640	626	261.5	(155.7, 439.2)
CQM157	C _{max} (ng/mL)	28.9	46.8	61.7	(39.1, 97.3)
	AUC _t (h*ng/mL)	1050	1330	78.9	(48.8, 127.6)
	AUC _{inf} (h*ng/mL)	629	1530	41.0	(24.9, 67.5)
BHS697	C _{max} (ng/mL)	13.0	22.8	56.7	(34.4, 93.5)
	AUC _t (h*ng/mL)	252	319	78.9	(51.8, 120.4)
	AUC _{inf} (h*ng/mL)	320	381	84.0	(54.3, 129.9)

Source: EDR 5.3.3.3 Study QBGI398-107 report Table 25.

Table 14. TEAEs leading to dose modification stratified by hepatic function categories.

Dose Modification	Normal (n=53)	Mild HI (n=50)	Moderate HI (n=4)
TEAEs leading to dose interruption	62.3% (33/53)	66% (33/50)	75% (3/4)
TEAEs leading to dose reduction	54.7% (29/53)	64.0% (32/50)	50% (2/4)
TEAEs leading to dose discontinuation	18.9% (10/53)	10% (5/50)	0%

Source: EDR 1.11.3 Response to FDA RFI-ClinPharm -23 Dec 2020.

Table 15. Simulated potency adjusted AUC_{activity} (μM*h) of infigratinib and BHS697, CQM157 for each renal impairment category in Study CBGI398X2204 at 125 mg, 100 mg, and 75 mg.

NCI criteria	N	AUC _{activity} Geometric Mean and 90% CI		
		125 mg	100 mg	75 mg
Normal hepatic function	38	38.8 (22.6, 67.3)	31.0 (18.1, 53.9)	23.3 (13.5, 40.4)
Mild B1 hepatic impairment	29	57.0 (34.4, 115.0)	45.6 (27.5, 92.0)	34.2 (20.7, 69.0)
Mild B2 hepatic impairment	7	62.9 (42.1, 82.6)	50.3 (33.7, 66.1)	37.7 (25.2, 50.0)
Moderate hepatic impairment	5	77.4 (50.7, 127.5)	61.9 (40.6, 102.0)	46.4 (30.4, 76.5)

Source: EDR 1.11.3 Response to FDA RFI-ClinPharm -23 Dec 2020.

Other special populations: FDA agrees with the Applicant's position that no therapeutic

individualization is needed in the proposed indication based on demographic factors, including age (19-86 years), weight (36.4-169.0 kg), sex, and race (White, n= 405 [70.7%]; Black, n= 88 [15.4%]; Asian, n= 46 [8%]; and Other, n= 34, [5.9%]) .

6.2.2.3. Outstanding Issues

Data:

Not applicable.

The Applicant's Position:

There are no outstanding issues.

The FDA's Assessment:

There are outstanding issues related to identifying an optimized starting dosage (Section 6.2.2) and adequate DDI assessment (Section 6.3.2). A PMR to evaluate one or more alternative dosages to further optimize the starting dose in the general patient population within ongoing or planned trials in patients was issued. FDA also issued 5 PMRs and 1 PMC to assess the DDI potential of infigratinib with moderate CYP3A4 inhibitors and inducers, P-gp inhibitors, BCRP inhibitors, MATE1 substrates, and BCRP substrates.

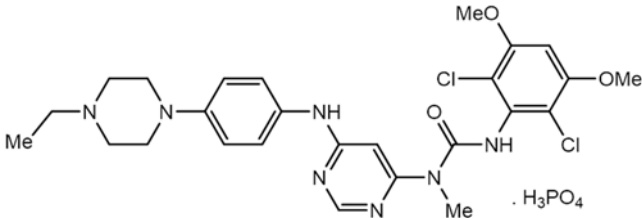
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

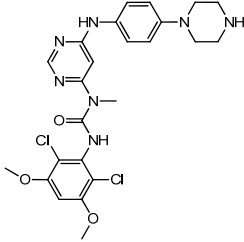
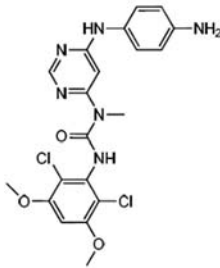
Data:

An overview of infigratinib clinical pharmacology characteristics is provided in Table 16 below.

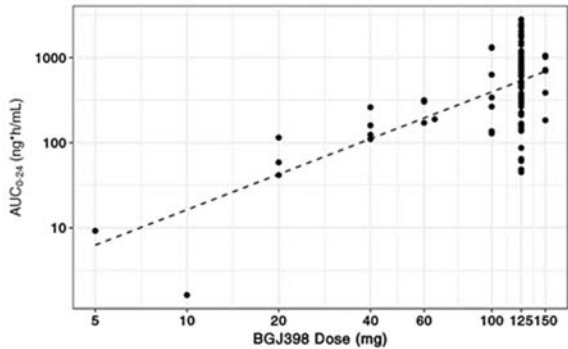
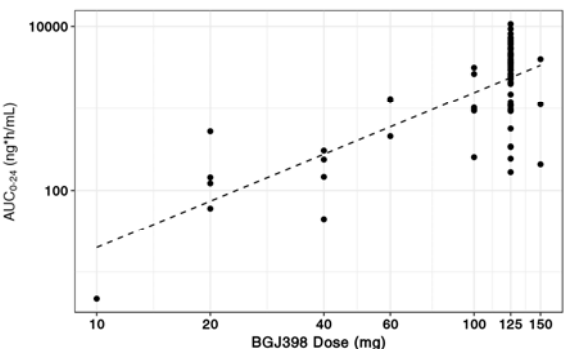
Table 16: Summary of Clinical Pharmacology Characteristics for Infigratinib

Physicochemical Properties									
Infigratinib chemical structure and molecular weight	Infigratinib ($C_{26}H_{31}Cl_2N_7O_3 \cdot H_3PO_4$, molecular weight [MW]=560.48 as free base)  $\cdot H_3PO_4$								
Aqueous solubility	Infigratinib has pH dependent solubility across the pH range of 1 to 6.8 <table border="1"> <thead> <tr> <th>Solvent</th><th>Solubility (mg/mL)</th></tr> </thead> <tbody> <tr> <td>0.1N HCl</td><td>0.094</td></tr> <tr> <td>2-Propanol</td><td>0.005</td></tr> <tr> <td>Ethanol</td><td>0.022</td></tr> </tbody> </table>	Solvent	Solubility (mg/mL)	0.1N HCl	0.094	2-Propanol	0.005	Ethanol	0.022
Solvent	Solubility (mg/mL)								
0.1N HCl	0.094								
2-Propanol	0.005								
Ethanol	0.022								

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	pH 6.8 Buffer Water	<0.001 1.3																																
Active metabolites chemical structure and molecular weight	BHS697 (C ₂₄ H ₂₈ Cl ₂ N ₇ O ₃ , MW=532.16) 	CQM157 (C ₂₀ H ₂₁ Cl ₂ N ₆ O ₃ , MW=463.10) 																																
Pharmacology																																		
Mechanism of action	Infigratinib is an orally available, potent, selective ATP-competitive inhibitor of inhibitor fibroblast growth factor receptor (FGFR) 1-3. Kinase selectivity in biochemical assays (IC ₅₀) and in vitro binding to FGFRs (K _d): FGFR1 IC ₅₀ =1.1 nM, K _d =0.53 nM FGFR2 IC ₅₀ =1 nM, K _d =1.2 nM FGFR3 IC ₅₀ =2 nM, K _d =0.7 nM																																	
Active moiety	The two major circulating metabolites (>10%) are BHS697 and CQM157. BHS697 contributes approximately 16% to 33% of FGFR1-3 inhibition. CQM157 contributes approximately 9% to 12% of FGFR1-3 inhibition.																																	
QT/QTc prolongation	Based on PK-ECG PK/PD modeling, infigratinib treatment has no clinically relevant effect (ie, >10 ms) on QTc interval.																																	
General Information																																		
Bioanalytical assay	Infigratinib bioanalytical assays (LC-MS/MS) were developed to measure the concentration of infigratinib in the clinical studies in this NDA.																																	
Patient PK vs. Healthy Subject PK	Infigratinib PK parameters after a single 125 mg dose: <table><tr><td></td><td colspan="3">Mean (%CV)</td></tr><tr><td>PK parameter</td><td>Healthy</td><td>Oncology</td><td>Cholangiocarcinoma</td></tr><tr><td>AUC_{0-24hr} (ng*hr/mL)</td><td>532 (97.0) n=20</td><td>768 (80.7) n=41</td><td>1467 (54.2) n=16</td></tr><tr><td>C_{max} (ng/mL)</td><td>68.4 (75.0) n=20</td><td>85.5 (62.4) n=45</td><td>154.7 (66.2) n=20</td></tr></table> Population derived or observed infigratinib PK parameters at steady state after 125 mg dosing: <table><tr><td></td><td colspan="3">Geo Mean (Geo %CV)</td></tr><tr><td>PK parameter</td><td>Healthy</td><td>Oncology</td><td>Cholangiocarcinoma</td></tr><tr><td>AUC_{0-24hr,ss} (ng*hr/mL)</td><td>1533.640 (155.963) n=157</td><td>3230 (59.4) n=25</td><td>4545.774 (5.880) n=79</td></tr><tr><td>C_{max,ss} (ng/mL)</td><td>87.567 (133.661) n=157</td><td>214 (50.9) n=35</td><td>230.059 (10.126) n=79</td></tr></table>			Mean (%CV)			PK parameter	Healthy	Oncology	Cholangiocarcinoma	AUC _{0-24hr} (ng*hr/mL)	532 (97.0) n=20	768 (80.7) n=41	1467 (54.2) n=16	C _{max} (ng/mL)	68.4 (75.0) n=20	85.5 (62.4) n=45	154.7 (66.2) n=20		Geo Mean (Geo %CV)			PK parameter	Healthy	Oncology	Cholangiocarcinoma	AUC _{0-24hr,ss} (ng*hr/mL)	1533.640 (155.963) n=157	3230 (59.4) n=25	4545.774 (5.880) n=79	C _{max,ss} (ng/mL)	87.567 (133.661) n=157	214 (50.9) n=35	230.059 (10.126) n=79
	Mean (%CV)																																	
PK parameter	Healthy	Oncology	Cholangiocarcinoma																															
AUC _{0-24hr} (ng*hr/mL)	532 (97.0) n=20	768 (80.7) n=41	1467 (54.2) n=16																															
C _{max} (ng/mL)	68.4 (75.0) n=20	85.5 (62.4) n=45	154.7 (66.2) n=20																															
	Geo Mean (Geo %CV)																																	
PK parameter	Healthy	Oncology	Cholangiocarcinoma																															
AUC _{0-24hr,ss} (ng*hr/mL)	1533.640 (155.963) n=157	3230 (59.4) n=25	4545.774 (5.880) n=79																															
C _{max,ss} (ng/mL)	87.567 (133.661) n=157	214 (50.9) n=35	230.059 (10.126) n=79																															

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Steady-state exposure at the proposed dosing regimen	Steady-state is achieved within 15 days of QD dosing. At 125 mg QD (3 weeks on/1 week off) in cholangiocarcinoma patients the observed exposure was: Infigratinib • $AUC_{0-24hr}=6284 \text{ ng*hr/mL}$ (42 %CV), n=8 • $C_{max}=330 \text{ ng/mL}$ (49 %CV), n=11 BHS697 • $AUC_{0-24hr}=1027 \text{ ng*hr/mL}$ (59 %CV), n=8 • $C_{max}=52 \text{ ng/mL}$ (63 %CV), n=11 CQM157 • $AUC_{0-24hr}=431 \text{ ng*hr/mL}$ (59 %CV), n=7 • $C_{max}=20 \text{ ng/mL}$ (78 %CV), n=11
Minimal effective dose or exposure	Unknown
Maximum tolerated dose	125 mg QD continuous
Dose Proportionality	Following multiple dosing, infigratinib exposures increased more than dose proportionally across the dose range of 5 mg to 150 mg once daily. Infigratinib exposure accumulated significantly following repeated dosing (0.79 to 8.00-fold, with 8.00-fold at the 125 mg 3 weeks on/1 week off regimen). Day 1- BGJ398 - AUC_{0-24} vs. Dose  Day 15- BGJ398 - AUC_{0-24} vs. Dose 

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Accumulation	Following once daily dosing at steady state in patients with cholangiocarcinoma (mean [%CV] for infigratinib): - AUC_{0-24hr} ratio=5.08 (38.5 %CV) - C_{max} ratio=7.71 (113.2 %CV)
Variability	Following 125 mg QD (3 weeks on/1 week off) in cholangiocarcinoma patients, inter-subject variability (%CV) was 42.0% and 48.6% for steady-state AUC and C _{max} , respectively.
Absorption	
Bioavailability	Absolute bioavailability not assessed. Metabolite ID data from hADME study (QBGJ398-101) indicates the infigratinib fraction absorbed is approximately 69%.
T _{max}	Median (range) T _{max} =6 hr (2-7)
Food effect	High-calorie, high-fat and low-calorie, low-fat
	GLSM Ratio (%) (90% CI)
	Infigratinib PK ParameterFMI I Low-calorie, Low-fat vs FastedFMI I High-calorie, High-fat vs FastedFMI III High-calorie, High-fat vs Fasted
	AUC _{inf} 1.66 (1.33, 2.07)2.24 (1.77, 2.84)1.81 (1.51, 2.17)
	C _{max} 1.91 (1.49, 2.45)1.77 (1.38, 2.28)1.62 (1.29, 2.04)
	Administration of infigratinib with food results in significant increase in the PK of infigratinib. Infigratinib should be coadministered 1 hour before or 2 hours after a meal.
Distribution	
Volume of distribution (Vd)	Plasma protein binding for infigratinib and its metabolites: Infigratinib: 98.2% BHS697: 98.7% CQM157: 99.5% Brain to plasma ratio (AUC _{inf})=0.682 in rats after a single oral dose. The mean apparent Vd in cholangiocarcinoma patients on Day 1 was 1247 L (145 %CV). The population predicted steady state mean, based on population PK, was 1180 L (83.0 %CV).
Substrate of transporter systems	Infigratinib is a substrate for P-gp and BCRP
Elimination	
Terminal elimination half-life and clearance	Following 125 mg of infigratinib The mean (%CV) half-life of infigratinib in oncology patients at steady state is 11.6 hr (32.0%) and 5.77 hr (44.7 %CV) after a single dose. The mean (%CV) half-life of infigratinib in cholangiocarcinoma patients after a single dose is 6.3 hr (20.4 %CV). The median (min, max) half-life at steady state of BHS697 and CQM157 in oncology patients is 29.1 hr (15.5, 146) and 52.8 hr (26.1, 313), respectively. The steady state apparent clearance (CL/F) is approximately 24.2 L/hr (52.8% CV) in cholangiocarcinoma patients

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Metabolism	Infigratinib is primarily metabolized by CYP3A4 (94% contribution of total clearance) with minor contributions by flavin containing monooxygenase (FMO) enzymes (6% contribution of total clearance). Metabolism of BHS697 is mediated via O-demethylation and metabolism of CQM157 is mediated by N-acetylation and O-demethylation.
Excretion	Based on the mass balance study, 77.3% of the dose is recovered in feces (3.43% as unchanged) and 7.22% in urine (1.90% as unchanged), supporting extensive metabolism.
Drug interaction liability	Infigratinib Metabolism - As victim: primarily metabolized by CYP3A4 Transporters - As victim: P-gp and BCRP substrate Other - As victim: acid reducing agents due to pH dependent solubility of infigratinib
Exposure-Response	
Efficacy	No exposure measures were statistically significant predictors of either OR or PFS. This lack of a significant exposure-response (E-R) relationship may be due to the relatively small sample size of patients included in these analyses.
Safety	Statistically significant E-R relationships were identified for hyperphosphatemia and eye disorders (excluding CSR/RPED). Higher infigratinib exposure resulted in higher probability of hyperphosphatemia and eye disorders (excluding CSR/RPED). Stochastic simulations to predict the probability of hyperphosphatemia or eye disorders (excluding CSR/RPED) when administering 50, 75, 100, and 125 mg 3 weeks on/1 week off showed a minimal change in the probability of these events; thus, supporting the appropriateness of the 125 mg 3 weeks on/1 week off dosing regimen.
AUC ₀₋₂₄ =area under the concentration-time curve from time 0 to 24 hours postdose; BCRP=breast cancer resistance protein; CL/F=apparent clearance; C _{max} =maximum plasma concentration; CSR/RPED=central serous retinopathy/retinal pigment epithelium detachment; E-R=exposure-response; FMI I=final market image formulation I; FMI III=final market image formulation III; GeoMean=geometric mean; LC-MS/MS=liquid chromatography tandem mass spectrometry; P-gp=p-glycoprotein, T _{max} =time to maximum concentration; Vd=volume of distribution. Source: Module 2.7.2, Table 3	

The Applicant's Position:

The PK properties of infigratinib and its active metabolites (BHS697 and CQM157) have been evaluated in healthy subjects and oncology patients. After single and repeat once daily dosing, infigratinib exposure increased in a more than dose proportional manner across the dose range of 5 mg to 150 mg (CBGJ398X2101). The mean steady state infigratinib AUC_{0-24hr} was 6284 ng*hr/mL (42 %CV) and C_{max} was 330 ng/mL (49 %CV) following 125 mg oral dosing in cholangiocarcinoma patients. Steady state was achieved after 2 weeks of daily dosing, and the mean accumulation ratio ranged from 0.79 to 8-fold, with 8-fold at the 125 mg 3 weeks on/1 week off regimen.

Absorption: Following oral administration of infigratinib in the fasted state, infigratinib absorption occurred at a median peak plasma concentration (T_{max}) of 6.0 hours (range 2 to 7 hours) in cholangiocarcinoma patients. Effect of food: administration of infigratinib with food increased the exposure of infigratinib AUC_{inf} by 1.7 to 2.2-fold. Metabolite ID data from hADME study (QBGJ398-101) indicates fraction absorbed is approximately 69%.

Distribution: The population derived apparent volume of distribution was 1180 L (83.0 %CV). Infigratinib, BHS697, and CQM157 are >96% bound to human plasma proteins. Following a single oral dose of [^{14}C]-infigratinib in healthy subjects, the blood-to-plasma ratio of [^{14}C]-radioactivity was 0.88 through 168 hours postdose. The ex vivo plasma protein binding of infigratinib, BHS697, CQM157, and BQR917 was approximately 99% in healthy subjects (QBGJ398-107).

Elimination: The mean half-life of infigratinib at steady state in cholangiocarcinoma patients was 11.6 h. The observed mean apparent clearance (CL/F) at steady state in cholangiocarcinoma patients was 24.2 L/h (52.8 %CV).

Metabolism: Infigratinib is extensively metabolized, primarily via CYP3A4 (~94%) and minimal contribution by FMO (6%) enzymes. The most abundant species in human plasma was unchanged infigratinib with 37.87% of dose, followed by a mixture of BHS697/M25/M24 (34.4% of dose), and M35 (27.36% of dose), while M27 and an unknown metabolite were minor components in plasma (0.31% and 0.06% of dose, respectively). CQM157 was not detected in the metabolite identification assays which had been shown to be in significant quantities (>10% of parent) in other clinical studies. Evidence of in process metabolite decomposition from CQM157 to M35 was found, as a result, the true plasma concentration of CQM157 was likely much higher than indicated by experimental data from this metabolite identification assay. Quantification of non-radiolabeled infigratinib and its metabolites showed that the metabolite to parent ratios ($AUC_{metabolite}/AUC_{infigratinib}$) were: 0.80, 0.26 for CQM157 and BHS697, respectively, supporting that CQM157 was formed in significant quantities and that in process degradation in the metabolite identification assay occurred. Overall, metabolites BHS697 and CQM157 are found at >10% of parent in human plasma samples.

Excretion: Following a single dose of [^{14}C]-infigratinib in healthy male subjects, approximately 84.5% of the radioactive dose was recovered, with 77.3% of the dose from feces and 7.22% from urine. Fecal and renal excretion of infigratinib as unchanged parent was minimal (3.43% of dose and 1.90% of dose, respectively) indicating extensive metabolism.

Effects of other drugs on infigratinib: Infigratinib is the substrate of CYP3A. Potent inhibition of both CYP3A results in a substantial increase in infigratinib exposure, and coadministration of infigratinib with potent inhibitors of CYP3A is not recommended. Likewise, drugs that are potent inducers of CYP3A may result in lower plasma exposures of infigratinib and lead to

reduced therapeutic effect; therefore, coadministration with potent inducers is not recommended.

Infigratinib is subject to pH dependent solubility, and coadministration of proton pump inhibitors may result in lower plasma exposures of infigratinib and lead to reduced therapeutic effect; therefore, coadministration with proton pump inhibitors is not recommended. Instead, gastric acid reducing agents, H₂-antagonists or antacids, may be administered. Infigratinib should be taken ≥ 2 hours before or 10 hours after dosing with H2RA. Antacids may be taken at least 2 hours before or after infigratinib dosing

Infigratinib is likely to be a P-gp and/or BCRP substrate and can be categorized as a low-solubility, moderate to high permeability compound. Consequently, it cannot be excluded that the rate and/or extent of infigratinib absorption is impacted by coadministered inhibitors of P-gp and/or BCRP. Infigratinib is unlikely to be a substrate of OATP, OAT, or OCT uptake transporters. The metabolite CQM157 is likely to be a substrate for P-gp (MDR1) and BCRP; however, because CQM157's contribution to the overall pharmacological activity is less than 50%, it is not anticipated that transport of CQM157 by P-gp is of clinical relevance. CQM157 and metabolite BHS697 are not substrates of OATP1B1 or OATP1B3.

Effects of infigratinib on other drugs: Infigratinib was shown to inhibit CYP3A4 in vitro; however, the drug-drug interaction (DDI) study with midazolam showed no clinically relevant impact of infigratinib on midazolam PK. Therefore, CYP3A4 substrates may be coadministered with infigratinib.

Infigratinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2, MATE1, and MATE-2K at clinically relevant concentrations. Infigratinib inhibited BCRP; therefore, clinical interactions with sensitive BCRP probes cannot be excluded. The metabolites BHS697 and CQM157 have a low potential to inhibit OATP1B1, OATP1B3, P-gp, or BCRP at clinically relevant concentrations.

The FDA's Assessment:

FDA generally agrees with the Applicant that the PK properties of infigratinib and its active metabolites (BHS697 and CQM157) were adequately characterized, except for the following:

1. **DDI Assessment:** The FDA does not agree with the Applicant that the DDI risk has been adequately assessed for infigratinib. See Section 6.3.2.3 for more details.
2. **QT Assessment:** The FDA does not agree with the Applicant's conclusion that "infigratinib does not result in a clinically relevant (> 10 msec) mean increase in the QTc interval" given the lack of support from the submitted concentration-QT assessment. In addition, the QT assessment does not cover the increases in infigratinib exposure with concomitant use of strong CYP3A4 inhibitors, while there were concentration-dependent effects in the in vitro hERG study and in clinical studies. The following conclusion is included in the infigratinib

labeling for QT:

At the recommended dosing regimen, Infigratinib does not result in a large mean increase (i.e. >20 msec) in the QTc interval. The QT effect of infigratinib at higher exposures associated with CYP3A4 inhibition has not been studied.

Refer to QT-IRT review for more details.

3. **PK parameters:** The Applicant proposed PK parameters are mixed assessments by noncompartmental analysis (NCA) as well as the population PK modeling from both Study CBGJ398X2204 in patients with cholangiocarcinoma as well as from Study 2101 in patients with solid tumors. On February 12, 2021, the Applicant provided the following updates in response to FDA IR sent on February 7, 2021, where the PK parameters were calculated estimated via NCA of the simulated hourly PK data from population PK model for the 79 patients with PK data in Study CBGJ398X2204.

Table 17. NCA estimated PK parameters of infigratinib and active metabolites BHS697, CQM197 based on individual PK^a estimates in patients with cholangiocarcinoma in Study CBGJ398X2204.

PK Parameter	Infigratinib GeoMean (%CV)		BHS697 GeoMean (%CV)		CQM197 GeoMean (%CV)	
	Single Dose N=79	Steady State N=79	Single Dose N=79	Steady State N=79	Single Dose N=79	Steady State N=79
AUC _{0-24hr} (ng*hr/mL)	794.74 (50.94)	3780.36 (58.75)	143.11 (45.34)	717.49 (55.02)	409.59 (57.56)	428.38 (71.58)
C _{max} (ng/mL)	66.96 (57.62)	202.20 (50.72)	9.81 (47.86)	35.47 (48.73)	21.80 (57.39)	20.12 (67.94)
T _{max} (h) ^b	4 (1-12)	5 (1-9)	4 (2-22)	4 (2-10)	10 (2-27)	7 (2-11)
t _{1/2} (h)	15.03 (19.80)	33.54 (39.19)	19.13 (26.77)	47.64 (30.97)	52.03 (26.91)	76.41 (52.30)
V/F (L)	2591.39 (44.06)	1600.16 (33.35)	N/A	N/A	N/A	N/A
CL/F (L/h)	119.50 (59.94)	33.07 (58.75)	N/A	N/A	N/A	N/A

^a Population PK model was using updated model with inclusion of hepatic and renal covariates.

^b Values for T_{max} are median (min, max).

Source: Response to FDA RFI-ClinPharm -12 Feb 2021.

The geometric mean results of AUC_{0-24hr}, t_{1/2}, V/F, and CL/F at steady state in the above Table 8 are verified by FDA and have been included in the labeling. Given the large shrink of V₂ in the population PK modeling that may cause an inaccuracy in estimation of steady state C_{max} and T_{max}, labeling included the original NCA results instead of the population PK results in Table 8, as the following Table 9. Of note, the Applicant reported steady state AUC_{0-24hr} as 6284 ng*hr/mL (42 %CV) and C_{max} as 330 ng/mL (49 %CV), as well as the 5- to 7- fold accumulation ratio, was based on arithmetic mean (CV%) results, not geometric mean (CV%) results as shown in Table 16.

Table 18. Geometric Mean (%CV) Exposure of Infigratinib and Active Metabolites in the labeling.

	Infigratinib	BHS697	CQM157
$C_{\max}$ (ng/mL)	282.5 (54%)	42.1 (65%)	15.7 (92%)
AUC _{0-24hr} (ng*hr/mL)	3780 (59%)	717 (55%)	428 (72%)

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Supportive evidence is provided by the data from the first-in-human dose escalation/dose expansion Study CBGJ398X2101 in patients with advanced solid malignancies with any FGFR mutation, amplification, or gene fusion, for whom no effective standard therapy exists. A total of nine dose levels and three different dose schedules were utilized in the dose escalation part and dose expansion part of the study. Eight dose levels were administered on the once daily continuous 28-day cycle schedule and one dose level was administered on the twice a day continuous 28-day cycle schedule. The expansion part included 125 mg on the once daily continuous 28-day cycle schedule and 125 mg on the once daily 3 weeks on/1 week off schedule. Of note, the 3 weeks on/1 week off schedule was first explored in treatment Arm 3 and was further administered for Arm 4 patients.

The dose of 125 mg on the once daily continuous regimen was declared as the MTD based on the emerging safety information, including dose-limiting toxicity (DLT) data from 34 of the 39 patients (non-bid regimen) included in the dose determining set guided by Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) principle. At this time, the risk of targeted and excessive toxicity at the MTD was 57.7% and 10.1%, respectively. One DLT of hyperphosphatemia was reported at the MTD. An alternative 3 weeks on/1 week off dosing schedule at 125 mg was introduced during the dose expansion part, which showed better tolerability. The 3 weeks on/1 week off at 125 mg was declared as RPTD.

In the dose escalation part, of the 92 patients, no complete response (CR) was observed and four patients had partial response (PR; one patient at 100 mg and three patients at 125 mg continuous dose).

Of the 173 patients treated at 125 mg continuous or intermittent schedule, CR was observed in two patients (1.2%) and 22 patients (12.7%) had PR. The overall response rate, ORR (95% CI) and disease control rate, DCR (95% CI), was 13.9% (9.10%, 19.94%) and 49.1% (41.47%, 56.83%), respectively.

NDA 214622 Multi-disciplinary Review and Evaluation Infigratinib (Truseltiq)

Pharmacokinetic-pharmacodynamic (PK/PD) analyses were conducted to assess the exposure-response (E-R) in terms of exposure-efficacy and exposure-safety in Study CBGJ398X2204. PK data across Phase 1 and Phase 2 studies were integrated into the population PK model to subsequently estimate exposure measures for each patient in CBGJ398X2204.

Exploratory analysis of the data showed that there appears to be a dose-related incidence, based on the average daily infigratinib AUC_{0-24hr} and percent of patients with overall response (OR). However, the sample size in the analysis population was small, with $n=16$ patients in each quartile of exposure.

The effect of average daily infigratinib and metabolite exposures (C_{trough} , C_{max} , C_{avg} , and AUC_{0-24hr}) on the probability of OR was evaluated using linear logistic regression models based on exploratory graphical displays. None of the exposure measures evaluated were found to be statistically significant predictors ($\alpha = 0.05$) of the probability of OR. The E-R modeling accounted for dose reductions/interruptions by determining the average daily infigratinib exposure. The lack of a significant E-R relationship may be due to the relatively small sample size of PK/PD data available in the overall analyses.

The E-R analysis of infigratinib and adverse events showed that relationship between infigratinib overall activity AUC_{0-24hr} and hyperphosphatemia. A higher log-transformed overall activity AUC_{0-24hr} was associated with a higher risk of hyperphosphatemia as indicated by the hazard ratio for the effect of log-transformed overall infigratinib daily AUC_{0-24hr} on time to first hyperphosphatemia. This indicates that with increasing log-transformed infigratinib overall exposure, or more specifically, for each increase of $1 \text{ nM} \times \text{h}$ of log-transformed overall infigratinib AUC_{0-24hr} , the predicted hazard for hyperphosphatemia was increased by 59%.

Stochastic simulations were performed to predict the expected outcomes for probability of hyperphosphatemia for 50, 75, 100, and 125 mg once-daily infigratinib dosing regimens utilizing 28-day cycles (3 weeks on/1 week off). While the probability for hyperphosphatemia is expected to be fairly high after the administration of 125 mg infigratinib (76.7%), the median probability of hyperphosphatemia across the simulated dose range of 50 to 125 mg on Day 20 ranges from 61.6% to 75.9% indicating that even a starting dose of 100 mg infigratinib (median probability of hyperphosphatemia on Day 20 of 72.6%) would mitigate the risk of hyperphosphatemia only minimally.

The Applicant's Position:

The safety and efficacy data in the CBGJ398X2101 and the E-R analysis from CBGJ398X2204 support the appropriateness of the dose for infigratinib of 125 mg 3 weeks/on 1 week/off.

The FDA's Assessment:

Based on review of the available data, the recommended dosage is not adequately justified

from a clinical pharmacology perspective, and uncertainty remains regarding whether the proposed recommended dosage of infigratinib as 125 mg 3 weeks/on 1 week/off, is optimized for safety and efficacy. Refer to Section 6.2.2.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The dose and dosing regimen of 125 mg 3 weeks on/1 week off in CBGJ398X2204 was based on the identified recommended Phase 2 dose from the dose escalation study CBGJ398X2101, and further supported by the E-R analyses conducted from the data in CBGJ398X2204.

Given the high interindividual variability of infigratinib exposure, a starting dose of 125 mg/day provides all patients the opportunity to quickly achieve an efficacious dose within two weeks (time to steady state exposure); while hyperphosphatemia, a class effect of FGFR inhibitors, provides an actionable on-target indicator for appropriate dose reductions. Exposure-response modeling and simulations for efficacy and safety provide an assessment of the appropriateness of the proposed dose regimen for study CBGJ398X2204, taking dose reductions into consideration. Exposure-response simulations also provide alternate dose levels to confirm that 125 mg 3 weeks on/1 week off does not significantly increase the probability of adverse events relative to lower doses.

The Applicant's Position:

Yes. The proposed dose of 125 mg 3 weeks on/1 week off is effective, manageable, and generally well tolerated.

The FDA's Assessment:

Based on review of the available data, the recommended dosage is not adequately justified from a clinical pharmacology perspective, and uncertainty remains regarding whether the proposed recommended infigratinib dosage of 125 mg 3 weeks/on 1 week/off, is optimized for safety and efficacy. Refer to Section 6.2.2.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Demographic Factors: Based on population analyses from Phase 2 (Study CBGJ398X2204) data, no clinically meaningful differences in infigratinib PK were observed based on age (23 to 81 years), sex, and race (White, Black, and Asian). As a result, there are no demographic characteristics that warrant dose adjustments.

Special Populations:

Hepatic impairment: Clinically significant exposure change (>2-fold) of infigratinib was observed in subjects with moderate hepatic impairment (the AUC_{inf} and C_{max} geometric mean ratio of infigratinib were 262% and 156%, respectively, in subjects with moderate hepatic impairment compared with subjects with normal hepatic function). The exposure of infigratinib in subjects with mild hepatic impairment was <2-fold (the AUC_{inf} and C_{max} geometric mean ratio of infigratinib were 186% and 178%, respectively, in subjects with mild hepatic impairment compared with subjects with normal hepatic function), and therefore may not require a dose adjustment. Similarly, in the population PK model that assessed the exposure of infigratinib in cholangiocarcinoma patients by NCI liver function criteria, a trend towards increased exposure with moderate liver function was observed and exposure was similar between patients with normal hepatic function and those with mild hepatic impairment (NCI B1, B2). Therefore, the dose of (b) (4) mg QD 3 weeks on/1 week off is considered appropriate for cholangiocarcinoma patients with mild hepatic function and a starting dose of infigratinib 75 mg QD 3 weeks on/1 week off is recommended for patients with moderate hepatic impairment.

Renal impairment: The population PK analysis assessed creatinine clearance as a covariate on infigratinib exposure. To investigate potential effects of renal function on the PK parameters, the exposure measures of the patients from CBGJ398X2204 were stratified by creatinine clearance category (normal: ≥90 mL/min, mild impairment: 60 to <90 mL/min, and moderate impairment 30 to <60 mL/min). Differences in the distributions of the individual and combined exposure measures between patients of the different renal impairment categories in CBGJ398X2204 showed no clinically relevant difference in AUC_{activity,ss} with impaired renal function. Patients with mild impaired renal function (n=20) had a geometric mean AUC_{activity,ss} (Geo %CV) of 36.1 (39.0), compared to 38.3 (26.0) in patients with normal renal function (n=52).

A study of the effects of moderate renal impairment on the PK of infigratinib is ongoing. The effect of severe renal impairment or renal dialysis in end-stage renal disease on infigratinib exposure is unknown.

The Applicant's Position:

Based on the assessment of intrinsic factors, a dose adjustment from 125 mg 3 weeks on/1 week off to 75 mg 3 weeks on/1 week off is recommended for patients with moderate hepatic impairment. (b) (4)

. The effects of moderate renal impairment will be determined from the ongoing study. The effects of severe hepatic impairment and severe renal impairment are unknown.

The FDA's Assessment:

FDA disagrees with the Applicant regarding the need for a starting dose adjustment in patients with mild or moderate renal impairment. FDA recommends a starting dose reduction to 100 mg

QD for patients with mild or moderate renal impairment. See Section 6.2.2.2.

FDA agrees with the Applicant that a starting dose reduction to 75 mg QD is needed for patients with moderate hepatic impairment. FDA disagrees with the Applicant regarding the need for a starting dose adjustment in patients with mild hepatic impairment. FDA recommends a starting dose reduction to 100 mg QD for patients with mild hepatic impairment. See Section 6.2.2.

FDA agrees with the Applicant that the effects of severe hepatic and renal impairment on the PK of infigratinib are unknown. The dosing recommendations for patients with severe hepatic impairment or severe renal impairment have not been established.

FGFR2 alterations and treatment response:

FDA explored the association between FGFR2 fusions or other rearrangements and treatment response in patients included in the primary efficacy population (N=108) in the CBGJ398X2204 trial. A total of 106 patients (of 108) had tumors harboring either FGFR2 fusions (n=88) or other rearrangements (n=18) as determined by a variety of local tests or by a central NGS test (Table 71– Appendix 19.4.5). For 2 patients, the distinction between a fusion or other rearrangement could not be made. BICC1 was the most common fusion partner. Many other partners, the majority not recurrent, were identified. Exploratory analysis of tumor response by alteration type showed an ORR of 23.9% in the subgroup of patients with tumors harboring fusions and of 22.2% in the subgroup of patients with tumors harboring other rearrangements. Of note, kinase domain mutations associated with resistance to FGFR2 inhibitors (Goyal et al. 2017, Silverman et al. 2021) were identified in post-progression biopsies of 2 out of 4 individuals tested. A PMC to evaluate mechanisms of resistance will be requested (see Section 6.1.2). For additional details, definition of fusions vs. other (non-fusion) rearrangements in the study and individual listing of FGFR2 alterations see Appendix 19.4.5.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food effects: In the food effect studies with infigratinib, food enhanced the availability of infigratinib. Coadministration of infigratinib (100 mg, FMI I) with a high-fat, high-calorie meal increased infigratinib with by a 2.24-fold and 1.77-fold for AUC_{inf} and C_{max}, respectively, compared with the exposures achieved under fasted conditions (CBGJ398X2103). Subsequent to this increase, the metabolite CQM157 also showed an increase of 1.3-fold in AUC_{inf} and 1.35 in C_{max}, however the metabolite BHS697 exposure was similar when infigratinib was given in the fed or fasted state. In this same study, the coadministration of infigratinib (100 mg) with a low-fat, low-calorie meal increased infigratinib AUC_{inf} and C_{max} by 1.66-fold and 1.91-fold, respectively, relative to infigratinib in the fasted state. Similarly, coadministration of infigratinib

(125 mg, FMI III) with a high-fat, high-calorie meal increased infigratinib with a ratio of 1.81-fold for AUC_{inf} and 1.62-fold for C_{max} , compared with the exposures achieved under fasted conditions). As administration of infigratinib with food resulted in significant increase in exposure of infigratinib, infigratinib was administered 1 hour before or 2 hours after a meal in patient trials.

Potential for infigratinib to affect other drugs: There is, overall, a low potential for infigratinib to be a perpetrator of DDIs through human drug metabolizing enzymes or drug transporters. CYP3A4 was inhibited in vitro by infigratinib. Due to the high prevalence of drugs metabolized by CYP3A4, a clinical DDI study was performed to assess the impact of infigratinib on the PK of a midazolam (a sensitive CYP3A4 substrate). The plasma exposure (AUC_{inf} , AUC_{last} , and C_{max}) of midazolam, was minimally affected following administration with infigratinib. Midazolam mean exposure was reduced by ~10% (AUC_{0-t} and AUC_{0-inf}) when administered with infigratinib; no difference was observed in C_{max} . The exposure of 1-hydroxymidazolam increased by ~15%-19% in terms of AUC_{0-t} and AUC_{inf} . These results indicate that infigratinib is a weak CYP3A inhibitor in vivo. Therefore, infigratinib may be coadministered with CYP3A4 substrates.

Effects of other drugs on infigratinib: Infigratinib has the potential to interact with drugs that affect CYP3A4 and infigratinib is subject to pH dependent solubility. As such, clinical DDIs were conducted to provide guidance upon coadministration with agents that affect CYP3A4 or alter gastric pH.

Following simultaneous administration of infigratinib (125 mg) with rifampin under fasted conditions (preceded by 600 mg QD rifampin, for 9 days), infigratinib exposure (AUC_{inf}) was reduced by 56%, and similar decrease in exposure were observed for BHS698 and CQM157. Drugs that are strong inducers of CYP3A4 may result in lower plasma exposure of infigratinib and may lead to reduced therapeutic effect of infigratinib; therefore, the coadministration of these two agents is not recommended.

Upon coadministration of infigratinib (75 mg) with itraconazole under fasted conditions (preceded by 200 mg QD itraconazole, for 3 days), infigratinib exposure (AUC_{inf}) increased by 622%, while the metabolites BHS698 increase was less substantial and there was no change in CQM157 AUC_{inf} . Drugs that are strong inhibitors of CYP3A4 may result in significantly higher plasma exposure of infigratinib and may lead to adverse events; therefore, the coadministration of these two agents is not recommended.

Following simultaneous administration of infigratinib (125 mg) with lansoprazole under fasted conditions (preceded by 30 mg QD lansoprazole, for 4 days), infigratinib exposure (AUC_{inf}) was reduced by 45%, and similar decrease in exposure were observed for BHS698 and CQM157. Drugs that are proton pump inhibitors may result in lower plasma exposure of infigratinib due to decreased absorption and may lead to reduced therapeutic effect of infigratinib; therefore,

the coadministration of proton pump inhibitors and infigratinib is not recommended. If coadministration cannot be avoided, proton pump inhibitors should be avoided and replaced with H₂-antagonists or antacids. Infigratinib should be taken ≥ 2 hours before or 10 hours after doing with H₂-antagonists. Antacids should be taken at least 2 hours before or after infigratinib dosing.

Potential for drug transporter mediated drug interactions: Infigratinib is likely to be a P-gp and/or BCRP substrate and can be categorized as a low-solubility, moderate to high permeability compound. Consequently, it cannot be excluded that the rate and/or extent of infigratinib absorption is impacted by coadministered inhibitors of P-gp and/or BCRP. Infigratinib is unlikely to be a substrate of OATP, OAT, or OCT uptake transporters. The metabolite CQM157 is likely to be a substrate for P-gp (MDR1) and BCRP; however, because CQM157's contribution to the overall pharmacological activity is less than 50%, it is not anticipated that transport of CQM157 by P-gp is of clinical relevance. CQM157 and metabolite BHS697 are not substrates of OATP1B1 or OATP1B3.

Infigratinib has a low potential to inhibit P-gp, BSEP, OCT1, OCT2, MATE1 and MATE-2K at clinically relevant concentrations. Infigratinib inhibited BCRP; therefore, clinical interactions with sensitive BCRP probes cannot be excluded. The metabolites BHS697 and CQM157 have a low potential to inhibit OATP1B1, OATP1B3, P-gp, or BCRP at clinically relevant concentrations.

The Applicant's Position:

Overall, the data support avoiding the coadministration of infigratinib with a strong CYP3A4 inhibitor or inducer, avoid coadministration with proton pump inhibitors, and stagger the dosing of infigratinib with pH modifying agents (infigratinib should be taken ≥ 2 hours before or 10 hours after dosing with H₂-antagonists. Antacids may be taken at least 2 hours before or after infigratinib dosing). Also, infigratinib should be administered 1 hour before or 2 hours after a meal.

The FDA's Assessment:

Drug-drug interaction: FDA agrees with the Applicant's assessment and recommendation to avoid coadministration of infigratinib with a strong CYP3A4 inhibitors or inducers and proton pump inhibitors. FDA agrees with the Applicant's recommendation to stagger the dosing of infigratinib with pH modifying agents.

Weak CYP3A4 inhibitor/inducer: The effect of weak CYP3A4 inhibitors and inducers on infigratinib PK has been assessed in Study CBGJ398X2204 by comparing the steady state infigratinib exposure in patients concomitantly taking a weak inhibitor or inducer with that in patients who did not. Of the 79 patients with infigratinib exposure measures, 14 received concomitant weak CYP3A inducers and 15 of received concomitant weak CYP3A inhibitors.

Table 19 lists the results of median AUC_{0-24h} of infigratinib and potency adjusted $AUC_{activity}$ in Study CBGJ398X2204. Based on the results, concomitant use of a weak CYP3A4 inducer or weak inhibitor does not appear to result in a clinically significant change (> 20%) in AUC. Therefore, patients may be administered concomitant weak CYP3A4 inhibitors or inducers with infigratinib.

Table 19. PK model predicted infigratinib AUC at steady state in the presence or absence of weak CYP3A4 inhibitors or inducers in Study CBGJ398X2204, assuming a 125-mg dose.

PK Parameters ^a	Co-med Weak CYP3A4 Inhibitors		Co-med Weak CYP3A4 Inducers	
	Present	Absent	Present	Absent
Infigratinib AUC_{0-24h} (ng*h/mL)	5003 (3239, 6419)	4648 (3510, 6502)	5357 (4078, 7231)	4553 (3054, 6358)
$AUC_{activity}$ (nM*h)	51.4 (33.9, 65.9)	50.2 (40.3, 65.2)	51.7 (43.7, 69.4)	49.3 (36.9, 64.7)

^a AUC values are listed as median (1st quartile, 3rd quartile).

Source: Applicant follow-up response to FDA midcycle meeting 28 January 2021.

DDI risks to be assessed: The Applicant has not adequately assessed the following DDI risks with data from in vivo studies in patients or healthy subjects:

1. Moderate CYP3A4 inhibitor or inducer: Infigratinib is primarily metabolized by CYP3A in vitro. In a single dose drug interaction study in healthy subjects, infigratinib exposure increased by 7-fold when coadministered with a strong CYP3A inhibitor (itraconazole) and decreased by 50% when coadministered with a strong CYP3A inducer (rifampin). The risk of a moderate CYP3A inhibitor or inducer affecting the PK of infigratinib has not been evaluated.
2. BCRP inhibitor or substrate: Infigratinib is a BCRP inhibitor and substrate in vitro. Infigratinib is also a CYP3A moderate inhibitor and substrate in vitro. Infigratinib has demonstrated time-dependent PK with 5- to 8-fold accumulation ratio (AUC , C_{max}) at steady state following a 125 mg QD dose. The Applicant stated that the time dependent PK may be related to BCRP, as the dedicated DDI study has proved that CYP3A is unlikely the cause for time dependent PK as infigratinib did not inhibit midazolam (CYP3A sensitive substrate) at clinically relevant concentrations.
3. P-gp inhibitor: Infigratinib is a P-gp substrate in vitro. The risk of P-gp inhibitors increasing infigratinib plasma exposure leading to increased adverse reactions has not been ruled out.
4. MATE1 substrate: Infigratinib is a MATE1 inhibitor in vitro. The inhibition potential of the major metabolites on transporters (MATE, OCT) have not been assessed. Among 27 patients concomitantly taking metformin (MATE & OCT substrate) with infigratinib, a total of 3 patients have developed hypoglycemia. The Applicant did not have blood glucose data to evaluate whether concomitant use of infigratinib may lead to increased metformin exposure, leading to blood glucose level decreases and hypoglycemia.

Based on the above, the Applicant will need to assess the DDI potential with the above CYP3A inhibitors and inducers, and drug transporters in postmarketing studies. The labeling recommendations have also been updated to avoid concomitant use of infigratinib with moderate CYP3A inhibitors and inducers. No additional restrictions on concomitant use of P-gp inhibitors, BCRP inhibitors/substrates, or MATE/OCT substrates have been included in the labeling recommendations based on the limited in vitro data to date and lack of sufficient clinical safety, PK, or PD data in the clinical trials with infigratinib. The current in vitro data serve as a marker to indicate the need for further in vitro screens or clinical studies to confirm or rule out the risk for a potential drug interactions through these mechanisms. Labeling recommendations will be updated based on results from the above PMRs.

Food Effect:

The assessment of food effect is generally acceptable. The FDA agrees with the Applicant that infigratinib should be administered 1 hour before or 2 hours after a meal.

X

Lili Pan
Primary Reviewer

X

Jeanne Fourie Zirkelbach
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Data:

Table 20: Tabular Listing of All Clinical Studies

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
Studies to Support Efficacy and Safety								
PK, Efficacy Pivotal Study	CBGJ398X 2204 18 US, DE, TH, SG, ES, BE, TW	Determine efficacy (ORR, PFS, BOR, DOR, OS), safety and PK of infigratinib and PK of FMI III and FMI IV ORR by BICR	Phase 2, multicenter, single arm Uncontrolled Ongoing (160 subjects planned across all cohorts) 23JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles) Formulations FMI I, FMI III, and FMI IV	108 Cohort 1 subjects with FGFR2 fusions enrolled and treated as of 31MAR2020 cutoff date 41M/67F 53.4 (23-81) years	Advanced or metastatic CCA with FGFR2 gene fusions or other FGFR genetic alterations who failed or are intolerant to platinum-based chemotherapy	28-day cycles until disease progression, study termination, or other DC reason	Ongoing; CSR (pivotal)
Studies to Support Safety								
PK, BA	CBGJ398A 2104 1 US	Evaluate the BA, safety and tolerability of 2 formulations of infigratinib (FMI II and CSF capsules) and the PK of metabolites BHS697 and CQM157 AUC _{last} , AUC _{inf} , C _{max} , T _{max}	Phase 1, R, OL, XO Uncontrolled Completed (30 subjects) 31JUL2014	Infigratinib single PO doses under fasting conditions; 14-day washout between doses. Formulations FMI II and CSF; 125 mg. <u>Treatment Sequence 1 – FMI II, then CSF</u> <u>Treatment Sequence 2 – CSF, then FMI II</u>	30 enrolled and treated 23M/7F 35.4 (21-54) years	Healthy, 18-55 years of age	2 single doses	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK, BA	CBGJ398X 2103 1 US	Assess the effect of food on PK of single doses of FMI I, the relative BA of CSF and FMI I formulations under fasted conditions, and assess safety and food effect on PK and BA of metabolites BHS697 and CQM157 AUC _{last} , AUC _{inf} , C _{max} , T _{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, 4-period, fed and fasted Uncontrolled Completed (24 subjects) 08MAY2014	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI I and CSF; 100 mg. <u>Treatment A:</u> CSF fasted <u>Treatment B:</u> FMI I fasted <u>Treatment C:</u> FMI I with low-fat, low-calorie meal <u>Treatment D:</u> FMI I with high-fat, high-calorie meal	24 enrolled and treated 21M/3F 33.6 (22-55) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR
BA, PK	CBGJ398X 2105 1 US	Evaluate the BA and safety of 2 formulations of infigratinib (FMI II and CSF capsules) and determine PK of metabolites BHS697 and CQM157 AUC _{last} , AUC _{inf} , C _{max} , T _{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, fed and fasted Uncontrolled Completed (40 subjects) 16JUL2015	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI II and CSF. <u>Treatment A:</u> 125 mg CSF fasted <u>Treatment B:</u> 75 mg FMI II with low-fat, low-calorie meal <u>Treatment C:</u> 125 mg FMI II with low-fat, low-calorie meal <u>Treatment D:</u> 200 mg FMI II fasted	40 enrolled and treated 32M/8F 37.2 (22-54) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK, BA	CBGJ398X-2106 1 US	Evaluate the BA, PK, food effect, and safety of 2 formulations of infigratinib (FMI III and CSF capsules) AUC _{last} , AUC _{inf} , C _{max} , T _{max}	Phase 1, R, OL, XO, 4-treatment, 4-sequence, 4-period, fed and fasted Uncontrolled Completed (40 subjects) 13JAN2016	Infigratinib single PO doses; 14-day washout between doses. Formulations FMI III and CSF. <u>Treatment A:</u> 125 mg CSF fasted <u>Treatment B:</u> 75 mg FMI III fasted <u>Treatment C:</u> 125 mg FMI III fasted <u>Treatment D:</u> 125 mg FMI III with high-fat, high-calorie meal	40 enrolled and treated 32M/8F 36.8 (23-51) years	Healthy, 18-55 years of age	4 single doses	Complete; CSR
PK	QBGJ398-102 1 US	Determine effect of rifampin on PK of infigratinib and the safety and tolerability of infigratinib when administered with rifampin AUC _{0-t} , AUC _{0-inf} , AUC _{Extrap} , T _{max} , T _{last} , C _{last} , and C _{max}	Phase 1, OL, fixed-sequence, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 05DEC2018	Infigratinib single doses. <u>Period 1:</u> 125 mg infigratinib PO fasted on Day 1 <u>Infigratinib washout:</u> 13 days (Days 1-13) <u>Period 2:</u> 600 mg rifampin PO QD on Days 5-13; 125 mg infigratinib PO + 600 mg rifampin PO fasted on Day 14	20 enrolled and treated 17M/3F 37.3 (20-53) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 14)	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QBGJ398-103 1 US	Determine effect of itraconazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with itraconazole AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , T _{1/2} , CL/F, V ₂ /F	Phase 1, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 04DEC2018	Infigratinib single doses. <u>Period 1</u> : 75 mg infigratinib PO fasted on Day 1 <u>Infigratinib washout</u> : 14 days (Days 1-14) <u>Period 2</u> : 200 mg itraconazole PO QD on Days 12-14; 75 mg infigratinib PO + 200 mg itraconazole PO fasted, Day 15	20 enrolled and treated 10M/10F 40.5 (19-55) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 15)	Complete; CSR
PK	QBGJ398-104 1 US	Determine effect of lansoprazole on PK of infigratinib and the safety and tolerability of infigratinib when administered with lansoprazole AUC _{0-t} , AUC _{0-inf} , C _{max} , T _{max} , T _{1/2} , CL/F, V ₂ /F	Phase 1, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 03DEC2018	Infigratinib single doses. <u>Period 1</u> : 125 mg infigratinib PO fasted on Day 1 <u>Infigratinib washout</u> : 14 days (Days 1-14) <u>Period 2</u> : 30 mg lansoprazole PO QD on Days 11-14; 125 mg infigratinib PO + 30 mg lansoprazole PO fasted on Day 15; 30 mg lansoprazole PO QD on Days 16 and 17	20 enrolled and treated 15M/5F 41.0 (23-55) years	Healthy, 18-55 years of age	2 single doses (Day 1 and Day 15)	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QBGJ398-106 1 US	Determine effects of multiple, QD oral doses of infigratinib on the PK of single oral doses of midazolam and the safety and tolerability of infigratinib when administered with midazolam AUC _{0-t_r} , AUC _{0-inf} , C _{max}	Phase 1, single-dose, OL, fixed-sequence, 2-period, 2-treatment, drug-drug interaction Uncontrolled Completed (20 subjects) 18FEB2019	Infigratinib multiple doses. <u>Period 1</u> : single dose 2 mg midazolam PO fasted on Day 1 <u>Infigratinib washout</u> : 3 days (Days 1-3) <u>Period 2</u> : 125 mg infigratinib PO fasted overnight for 6 days (Days 4-9); single dose of 125 mg infigratinib + 2 mg midazolam PO fasted on Day 10	20 enrolled and treated 18M/2F 34.1 (19-45) years	Healthy, 18-55 years of age	7 days (Day 1 and Days 4-10)	Complete; CSR
PK	QBGJ398-101 1 US	Determine mass balance, routes and rates of elimination of total radioactivity, and PK of infigratinib and metabolites (CQM157, BHS697, and BQR917), the chemical structure of the metabolites, and the safety and tolerability of infigratinib C _{max} , T _{max} , C _{last} , T _{last} , λ _z , T _{1/2} , AUC _{last} , AUC _{inf} , total radioactivity in urine and feces	Phase 1, OL, single-radiolabeled dose, not randomized Uncontrolled Completed (8 subjects) 10DEC2018	Infigratinib single PO dose 125 mg (as free base) containing 150 µCi of [¹⁴ C] infigratinib (fasted)	8 enrolled and treated 8M/0F 34.4 (26-50) years	Healthy males, 18-55 years of age	Single dose	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK	QBGJ398-109 1 US	Evaluate PK, safety and tolerability of infigratinib FMI IV formulation AUC ₀₋₂₄ , AUC _{inf} , and C _{max} , AUC _{last} , %AUC _{extrap} , T _{max} , T _{1/2} , CL/F and V _z /F	Phase 1, OL, 1-period, PK Uncontrolled Completed (20 subjects) 12JUL2019	Infigratinib single PO dose 125 mg (fasted) FMI IV formulation	20 enrolled and treated 17M/3F 36.8 (19-53) years	Healthy, 18-55 years of age	Single dose	Complete, CSR
PK, PD	CBGJ398X-2102 22 US, ES, FR, IT, AU, BE, CA, DE, NL, SK, SG, CH	Determine MTD and/or RDE, safety and tolerability, PK, and preliminary antitumor activity Estimation of probability of DLT in Cycle 1	Phase 1b, multicenter, OL, dose escalation and expansion, PK Uncontrolled Completed (50 subjects) 02OCT2013	Infigratinib PO QD (3 weeks on/1 week off) + alpelisib QD (28-day cycles) Dose groups infigratinib + alpelisib (1) 20 mg + 300 mg (2) 20 mg + 400 mg (3) 40 mg + 300 mg (4) 75 mg + 300 mg (5) 90 mg + 300 mg (6) 100 mg + 300 mg (7) 125 mg + 300 mg	62 enrolled and treated 23M/39F 58.4 (30-78) years	Escalation: Advanced solid cancers with PIK3CA mutations Expansion: Advanced solid cancers (except CRC) with PIK3CA mutations with or without FGFR mutations, amplifications, or translocations	28-day cycles until disease progression study termination or other DC reason	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
PK, PD	CBGJ398X 1101 8 JP CN	Estimate MTD and/or RDE, safety and tolerability, PK, and preliminary antitumor activity Incidence rate and category of DLTs in Cycle 1	Phase 1, multicenter, OL, dose finding, dose-escalation and expansion Uncontrolled Complete (35-38 subjects) 19OCT2012	<u>Escalation</u> : Infigratinib PO, QD or BID: 50, 100, 125, 150, 175, 200 mg <u>Safety run in (Chinese only)</u> : ≤MTD/RDE for Japanese <u>Expansion (not done; study terminated)</u> : Infigratinib TBD (QD or BID) PO	9 enrolled and treated (Escalation: 6 Japanese subjects; Safety run in: 3 Chinese subjects) 8M/1F 56.4 (25-66) years	Escalation: Japanese subjects with advanced solid tumors with FGFR1 or FGFR2 amplification, FGFR3 mutation or other FGFR alteration for which no further standard therapy existed Safety run-in: Chinese subjects, same diagnosis as for Escalation	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR
PK, PD	CBGJ398X 2101 38 AT, FR, DE, IL, IT, SK, NL, SG, ES, TH, US	Determine MTD, RPTD, and schedule of infigratinib administration; preliminary antitumor activity in Arm 4; safety and tolerability at the RPTD; PK; determine optimal biological dose; evaluate potential predictive biomarkers	Phase 1, multicenter, OL, dose-finding Uncontrolled Completed (153 subjects) 09NOV2009	Infigratinib PO: 28-day dosing cycles Formulations: FMI I and CSF <u>Escalation</u> : Continuous QD: 5, 10, 20, 40, 60, 100, 125, 150 mg; BID: 50 mg <u>Expansion</u> : <i>Arms 1 and 2</i> : 125 mg, continuous QD <i>Arms 3 and 4</i> : 125 mg, 3 weeks on 1 week off	208 enrolled and treated 112M/96F 60.4 (25-86) years	Histologically/ cytologically confirmed advanced solid tumors carrying any FGFR mutation, amplification or gene fusion, for whom no effective standard therapy exists	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
		Incidence rates and categories of DLTs						
PK (intrinsic)	QBGJ398-107 1 US	Assess PK, safety, and tolerability of infigratinib in subjects with chronic hepatic impairment and matched healthy adults C_{max} , T_{max} , C_{last} , T_{last} , λ_z , $T_{1/2}$, AUC_{0-t} , AUC_{inf} , AUC_{Extrap} , CL/F , V_z/F	Phase 1, NR, OL, parallel-group Uncontrolled Completed (40 subjects) 27FEB2019	Infigratinib 125 mg PO, single dose, fasted	40 planned and treated 24M/16F 58.7 (35-79) years	Chronic hepatic impairment (Child-Pugh Class A or B); Matching healthy	Single dose	Complete, CSR
Efficacy	CBGJ398X2201 13 BE, CH, ES, NL, US	Assess anti-tumor activity (PFS, ORR, OS), safety and tolerability PFS rate at 6 months	Phase 2, multicenter, OL Uncontrolled Completed (34 subjects planned) 09DEC2013	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles)	26 enrolled and treated 16M/10F 53.7 (20-76) years	Recurrent glioblastoma and/or other glioma subtypes, with FGFR1-TACC1, FGFR3-TACC3 fusion and/or activating mutation in FGFR1, FGFR2, or FGFR3 gene	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Study Type	Study ID; # of Study Centers; Location	Study Objective(s); Primary Endpoint(s)	Study Design and Type of Control; Enrollment Status (Goal); FPFV	Test Product(s) ^a ; Dose Regimen; Route of Administration	Number of Subjects; M/F; Mean Age (Range)	Healthy Subjects or Diagnosis of Patients/Main Incl Criteria	Duration of Tx	Study Status; Type of Report
Efficacy	CBGJ398X US04 41 US	Assess clinical benefit (CR, PR, SD, OR, PFS, OS, DOR), safety and tolerability Clinical benefit rate (CR, PR, or stable disease ≥16 weeks for solid tumors)	Phase 2, OL, signal-seeking Uncontrolled Completed (70-90 subjects planned) 21JUL2014	Infigratinib 125 mg PO QD: 3 weeks on / 1 week off (28-day cycles)	85 enrolled 84 treated 37M/47F 60.2 (33-85) years	Solid tumor or hematologic malignancy or with a history/ evidence of TIO and FGF23-mediated hypophosphatemia with or without identification of an FGFR genetic alteration	28-day cycles until disease progression, study termination, or other DC reason	Complete; CSR

Abbreviations: BA=bioavailability; BICR=blinded independent central review; BID=twice daily; BOR=best overall response; CCA=cholangiocarcinoma; CR=complete response; CRC=colorectal cancer; CSF=Clinical Service Form; CSR=clinical study report; DC=discontinuation; DCR=disease control rate; DOR=duration of response; FGFR=fibroblast growth factor receptor; FMI=Final Market Image; Loc=location; MTD=maximum tolerated dose; NA=not applicable; NR=nonrandomized; OL=open-label; OR=overall response; ORR=overall response rate; OS=overall survival; PD=pharmacodynamic; PFS=progression-free survival; PK=pharmacokinetic(s); PO=oral; PR=partial response; QD=once daily; QOL=quality of life; R=randomized; SD=stable disease; TIO=tumor-induced osteomalacia; Tx=treatment; UCC=urothelial cell carcinoma; WT=wild type; XO=crossover.

^a Nomenclature for the investigational product has evolved over the development program. The current convention is to refer to the Final Market Image followed by the appropriate formulation by Roman numeral (ie, FMI I, FMI II, FMI III, FMI IV). This terminology is used with the exception that the protocol title remained unchanged.

Source: 5.2 Tabular Listing of Clinical Studies

NDA 214622 Multi-disciplinary Review and Evaluation Infigratinib (Truseltiq)

US: United States; DE: Denmark; TH: Thailand; SG: Singapore; ES: Spain; BE: Belgium; TW: Taiwan; FR: France; IT: Italy; AU: Australia; CA: Canada; NL: Netherlands; SK: Slovakia; CH: Switzerland; JP: Japan; CN: China; AT: Austria; IL: Israel.

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety of infigratinib are summarized in Table 20.

The FDA's Assessment:

FDA generally agrees with Applicant's description of the clinical trials considered in this review. The 108 patients of Cohort 1 of Study CBGJ398X2204 who had FGFR2 gene fusions/rearrangements form the basis of the primary analyses of safety and efficacy for this NDA.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study CBGJ398X2204

Trial Design

The Applicant's Description:

Basic Elements:

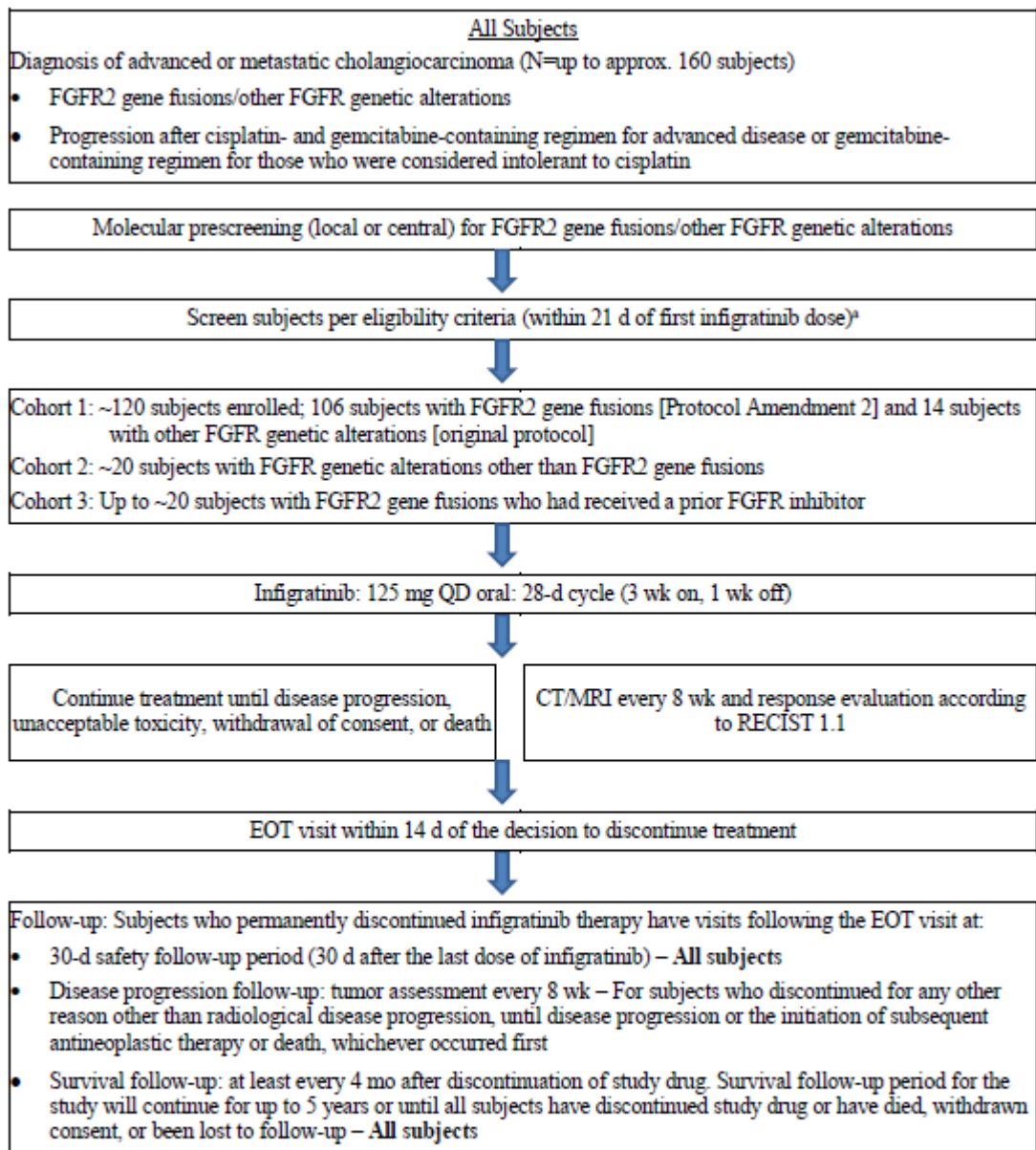
Study CBGJ398X2204 is an ongoing multicenter, open-label, 3-cohort, Phase 2 study evaluating infigratinib antitumor activity in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations (enrolled in Cohort 1). Eligible study participants were required to have documented evidence of FGFR gene alterations determined through molecular prescreening. Eligible study participants were also required to have received at least one prior treatment regimen containing gemcitabine with or without cisplatin for advanced/metastatic disease. Subjects had to have evidence of progressive disease following their prior regimen, or if prior treatment was discontinued due to toxicity, had to have continued evidence of measurable disease. Interim Analysis Set 2 for Cohort 1 is the primary efficacy analysis set for the data presented in this marketing application. The Interim Analysis Set 2 for Cohort 1 includes subjects in Cohort 1 with FGFR2 gene fusions who received ≥ 1 dose of infigratinib. As of the data cutoff for this interim analysis, 108 subjects with FGFR2 gene fusions in Cohort 1 received at least 1 dose of study drug. An overview of study design is provided in [Figure 8](#).

Trial location: Subjects were enrolled across 18 study centers (9 in the United States, 5 in Western Europe, and 4 in Asia).

Choice of control group: A control group was not included, given the lack of established therapy for this patient population.

Diagnostic Criteria: Histologically or cytologically confirmed cholangiocarcinoma.

Figure 8: CBGJ398X2204 Study Design



Abbreviations: CT=computed tomography; d=day; EOT=end of treatment; FGFR2=fibroblast growth factor receptor 2; mo=month; MRI=magnetic resonance imaging; QD=once a day; RECIST=Response Evaluation Criteria in Solid Tumors; wk=week.

* Screening assessments are completed within 21 days before the first dose of treatment, except for the radiological tumor assessment, which can be performed within 28 days before the first dose.

Source: CBGJ398X2204 CSR, Figure 1

Key Inclusion/Exclusion Criteria: This study includes adult subjects with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or other FGFR genetic alterations who failed or

were intolerant to gemcitabine-based antineoplastic treatment.

Main inclusion criteria:

- Histologically or cytologically confirmed cholangiocarcinoma at the time of diagnosis. Subjects with cancers of the gallbladder or ampulla of Vater are not eligible.
- Written documentation of local or central laboratory determination of the following FGFR gene alterations from a sample collected before infigratinib treatment:
 - Cohort 1: FGFR2 gene fusions.
 - Cohort 2: one of the following: (a) FGFR1 fusions, (b) FGFR3 fusions, or (c) FGFR1/2/3 mutation known to be an activating mutation.
 - Cohort 3: FGFR2 gene fusions (must receive prior treatment with an FGFR2 inhibitor).
- Evidence of measurable disease according to RECIST version 1.1.
- Receipt of at least one prior regimen containing gemcitabine with or without cisplatin. Subjects must have evidence of progressive disease after their prior regimen; if prior treatment was discontinued due to toxicity, subjects must have had continued evidence of measurable disease.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 (Subjects with ECOG PS of 2 may be considered on a case-by-case basis after discussion with QEDTherapeutics).

Main exclusion criterion: Prior treatment with an FGFR inhibitor or MEK inhibitor is not allowed, with the exception of Cohort 3 (Protocol Amendment 4), which requires prior FGFR inhibitor therapy.

Dose selection: Subjects received 125 mg QD of infigratinib on a 3-week on (21 day)/1-week off (7 day) schedule in 28-day cycles. This regimen was selected based on safety and MTD, efficacy, and PK modeling during dose escalation during an early Phase 1 study (CBGJ398X2101), further evaluated in an expansion cohort in that study, and then used in this registrational study and other ongoing studies.

Study treatments, Assignment to Treatment, and Blinding: This is an open-label, single-arm study. All subjects were assigned to receive oral infigratinib 125 mg once a day (QD) (administered as one 100-mg capsule and one 25-mg capsule) using a “3-weeks on, 1-week off” schedule for each 28-day treatment cycle.

Dose modification/discontinuation:

Efficacy-related dosing changes: None.

Safety-related dosing changes: For patients who did not tolerate the protocol-specified dosing schedule, dose adjustments were permitted in order to allow the patient to continue the study treatment. Each patient was to be allowed 3 dose reductions according protocol-specified dose modifications for AEs, with dose-level (DL) reductions to 100 mg (DL -1), 75 mg (DL -2), and 50 mg (DL -3). Dose reductions below 50 mg were not allowed. All dose modifications were to be based on the worst preceding toxicity. Following resolution of toxicity to baseline or Grade ≤ 1 , treatment was to be resumed at either the same or lower dose of study drug as per the criteria in the protocol. In addition, the study protocol included tabular dose reduction guidelines for management of mechanism-based toxicities, including hyperphosphatemia and ocular toxicity.

Administrative structure: Study CBGJ398X2204 was a Phase 2 study initiated by Novartis; Novartis implemented Protocol Amendment 2 to restrict enrollment of Cohort 1 to patients with FGFR2 fusions or rearrangements. Following implementation of Protocol Amendment 3, sponsorship was transferred to QED Therapeutics, Inc. The study was conducted across 18 study centers (9 in the US, 3 in Germany, 2 in Singapore, and 1 each in Thailand, Spain, Belgium, and Taiwan). Two additional centers enrolled a subject, but they are not included in this interim analysis. A blinded independent central review (BICR) committee was implemented to provide an independent assessment of radiographic response and progression. The BICR did not communicate with the sites about response assessments but was permitted to communicate with the imaging facilities whenever a technical issue required clarification.

Procedures and schedule: Patients were treated in 28 day cycles. Efficacy was assessed by evaluating for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST 1.1. Partial response (PR) and complete response (CR) are confirmed by repeat assessment at least 4 weeks after the criterion for response was first met. Survival status and use of new antineoplastic medications were followed at least every 4 months after discontinuation of study drug. Survival follow-up will continue for up to 5 years or until all subjects have discontinued study, died, withdrawn consent, or are lost to follow-up. Safety assessments were completed during each cycle.

Treatment compliance: The investigator or responsible study center personnel instructed subjects to take infigratinib exactly as prescribed to promote compliance. On the day of a scheduled visit to the clinic, the subject was to take the study drugs under the supervision of the Investigator or designee. All dosages prescribed and dispensed to the subject and all dose changes or missed doses during the study were recorded in the eCRF.

Subject completion, discontinuation, or withdrawal: Subjects were to be treated until unacceptable toxicity, disease progression, treatment is discontinued at the discretion of investigator or withdrawal of consent, or death. Subjects who withdrew from the study were not replaced regardless of reason for withdrawal. For patients who discontinued treatment for

reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments continued to be performed every 8 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

The FDA's Assessment:

FDA agrees with the applicant's description of the trial design for study CBJ398X2204. The detection of FGFR2 fusions or other rearrangements in tumor tissue by either local or central test was required to determine molecular eligibility. According to the central test classification rules, both FGFR2 fusions and other rearrangements must have had the breakpoint within the FGFR2 intron 17/ exon 18 hotspot. Further details on testing and results can be found in Section 19.4.5

Study Endpoints

The Applicant's Description:

Primary: Overall response in Cohort 1 assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The estimated overall response rate (ORR) is presented with corresponding 95% confidence interval (CI) based on the binomial distribution (Clopper-Pearson exact method) accompanied by duration of response (DOR) to allow for more complete characterization of the beneficial effect infigratinib.

Secondary:

- Overall response assessed by investigator; progression-free survival (PFS), best overall response (BOR), disease control assessed by investigator and by BICR according to RECIST 1.1; and overall survival (OS) (Cohort 1).
- Safety: Type, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs); and Tolerability: dose interruptions, reductions, and intensity (Cohort 1).
- Selected trough and 2-hour or 4-hour plasma concentration profiles and derived PK parameters of infigratinib and its metabolites (overall study).
- For FMI III and FMI IV: Plasma concentration profiles and derived PK parameters of FMI III and FMI IV (overall study).

Exploratory:

- Type, frequency, and severity of AEs and SAEs and tolerability (dose interruptions, reductions, and intensity) (Cohorts 2 and 3).
- PFS, overall response, BOR, response onset, and disease control assessed by the investigator per RECIST version 1.1, and OS (Cohorts 2 and 3).

- Deoxyribonucleic acid (DNA) sequencing of paired biopsies (tumor tissue) from subjects who progressed and analysis of cell free deoxyribonucleic acid (cfDNA) (overall study).

The FDA's Assessment:

FDA agrees with the applicant's description of the study endpoints. FDA's efficacy evaluation is based on the primary endpoint of overall response rate (ORR) by BICR according to RECIST v1.1, accompanied with the durability of response (DOR) by BICR. FDA considers disease control rate (DCR) to be an exploratory endpoint, not supportive of registration. Additionally, time-to-event endpoints of OS and PFS are not interpretable in a single arm study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical analysis plan (v3.0) was finalized prior to the conduct of the interim analysis and provides detailed statistical methodology for the analysis of data from study CBGJ398X2204 that is in the interim Clinical Study Report (CSR). The output data are presented in the Tables, Figures and Listings accompanying the CSR. The specifications for derived variable and datasets can be found in the ADaM Reviewer's Guide. This version of the SAP is based on the Clinical Study Protocol CBGJ398X2204 Version 6 (Amendment 5) dated 15-Jan-2020.

The assessment of efficacy for the NDA was conducted using the Interim Analysis Set 2 for Cohort 1, described as the second formal interim analysis after Amendment 3 in the protocol and SAP for Study CBGJ398X2204. The primary analysis set for the NDA includes subjects in Cohort 1 with FGFR2 gene fusions who received at least one dose of infigratinib. The cutoff date for this analysis (31 March 2020) allowed all subjects with FGFR2 gene fusions who received infigratinib at the time of the first formal interim analysis to have at least 10 months follow-up after their initial exposure to infigratinib. The Sensitivity Analysis Set for Cohort 1 includes subjects with FGFR2 gene fusions who received infigratinib at the time of the first formal interim analysis and subjects who had disease progression according to central imaging review or ended treatment by the cutoff date. Some analyses, including summary of demographic, baseline characteristics and disposition, and some key efficacy and safety analyses, were repeated on the Sensitivity Analysis Set. The primary objective is to evaluate efficacy as measured by confirmed ORR (central imaging review [BICR]). The estimated overall response rate (ORR) is presented with corresponding 95% confidence interval (CI) based on the binomial distribution (Clopper-Pearson exact method) accompanied by duration of response (DOR) to allow for more complete characterization of the beneficial effect of infigratinib. Secondary efficacy objectives are ORR (investigator assessment), OS, PFS (central imaging review and investigator assessment), BOR (central imaging review and investigator assessment), disease control rate (central imaging review and investigator assessment), and response onset and DOR (central imaging review and investigator assessment for confirmed responders only).

Table 21: Study CBJ398X2204 SAP Amendments Summary

Version/Date	Summary of Major Changes and Rationale
Original/ 09 NOV 2017	NA
V1.0/ 29 MAY 2019	- Revise the SAP to be consistent with the Protocol Version 5 (Amendment 4) (24-Apr-2019) - Clarify some statistical analysis details
V2.0/ 26 MAR 2020	Revise the SAP to be consistent with the Protocol Version 6 (Amendment 5) (15-Jan-2020)
V3.0/ 13 MAY 2020	More precisely specify analysis methods for overall response rate (ORR), time to response (TTR), and duration of response (DOR).

The FDA's Assessment:

FDA agrees with the applicant's description of the statistical analysis plan. The final version of the statistical analysis plan dated 13 May 2020 included justification for sample size based on estimation precision. This sample size justification appeared adequate from the FDA perspective as FDA does not consider inferential procedures in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response

Protocol Amendments

The Applicant's Description:

The study protocol was amended five times prior to the interim analysis. None of the changes impacted trial integrity of interpretation of the results. The table below describes the key changes made in each amendment.

Table 22: Study CBJ398X2204 Protocol Amendments

Number (date of internal approval)	Reasons for Amendment
00 (21 Feb 2014)	N/A (original protocol)
01 (11 Mar 2015)	- Entry criteria were modified to clarify subject eligibility and align with SOC treatment for cholangiocarcinoma. - Hyperphosphatemia management guidelines were updated to provide more detail regarding prophylaxis and how to modify infigratinib dose administration in response to elevated serum phosphorous levels. - Serum creatinine and creatinine clearance exclusion criteria were revised to align with current medical practice and provide consistency across infigratinib protocols. - Evaluations of cardiac function by ECHO/MUGA scan were added on Day 1 of Cycles 2, 3, and 4. - Allowed collection of tumor tissue at baseline and upon the development of acquired resistance to treatment as described in the optional companion sample

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	collection protocol. Two blood samples were also collected to test the potential value of circulating cfDNA.
02 (24 Jan 2017)	- Increased enrollment to approximately 120 subjects to (1) introduce a new drug formulation, FMI III, and (2) allow further evaluation of the safety and preliminary efficacy signal observed in the first 61 subjects enrolled. - Enrollment in Cohort 1 was restricted to subjects with intrahepatic cholangiocarcinoma with FGFR2 gene fusions. - FMI III replaced the former drug formulation (FMI I) for all subjects enrolled after implementation of Amendment 2. - PK, safety and tolerability data from the first 20 subjects treated with FMI III up to the end of Cycle 1 were assessed and compared with historical data from subjects treated with FMI I. Serial blood samples were collected from the remaining subjects to further characterize the PK properties of FMI III in this subject population. - Initiated independent review of radiologic assessments by an imaging CRO. - Updated biomarker strategy, including (1) added cfDNA sampling, (2) discontinued CA19-9 sample collection, (3) discontinued whole blood collection for exploratory germline analysis, and (4) removed language pertaining to Novartis optional companion sample collection protocol. - Reduced frequency of cardiac imaging at Cycles 3 and 4.
03 (19 Sep 2018)	Changed sponsor name from Novartis to QED Therapeutics and provided safety reporting information for the CRO working with QED Therapeutics.
04 (24 Apr 2019)	- Revised assessment of overall response for the primary endpoint for subjects with FGFR2 gene fusions from confirmation by investigator to confirmation by BICR; changed investigator assessment of overall response from a primary to a secondary objective. - Included interim analysis, to occur when subjects enrolled before Amendment 2 had potentially been followed up for ≥ 10 months after initial exposure to infigratinib. - Revised RECIST criteria guidelines to be consistent with published criteria. - Included 2 additional cohorts, allowing enrollment of subjects with known FGFR1, 2, or 3 activating mutation or FGFR1 or 3 fusions (Cohort 2) and subjects with FGFR2 gene fusions after previous treatment with gemcitabine-containing regimen followed by progression on an FGFR inhibitor (excluding infigratinib) (Cohort 3). - Included interim analysis for Cohort 3 when the first 10 subjects who received study treatment have the potential to complete their second scheduled scan (to determine if an additional 10 subjects will be added to the cohort.). - Clarified that 108 subjects with FGFR2 gene fusions will be included in Cohort 1, and this sample size is the basis of statistical analyses for this group. - Allowed another formulation of infigratinib (FMI IV) to be administered to subjects, with accompanying PK analysis and analysis comparing the 3 formulations administered. Subjects in Cohort 1 were transitioned to FMI IV when this formulation was available at the study center. - Extended follow-up for survival from 1 to 5 years after discontinuation of study treatment or until subjects died, withdrew consent, or were lost to follow-up. - Excluded subjects with history and/or current evidence of extensive tissue

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	calcification of the vascular system; modified criteria for interruption and re-initiation of infigratinib in accordance with QTc evaluation plan submitted to FDA; included OCT in the ophthalmic examination; revised PK sparse sampling times; revised and updated list of drugs to be used with caution on study and list of prohibited medication; added FGFR1/2/3 known activating mutations list for Cohort 2 inclusion criteria.
05 (15 Jan 2020)	Revised based on updates to standards for safety and study conduct for infigratinib; and added second interim analysis.

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol amendments. For further details regarding how hyperphosphatemia was managed, see Section 8.2.5.2 Hyperphosphatemia.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

Not applicable.

The Applicant's Position:

This clinical study was conducted in accordance with the International Council for Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The FDA's Assessment:

FDA acknowledges the Applicant's statement above and included in Section 5.2 of the CSR and Section 11.1 of the clinical protocol for the CBGJ398X2204 trial.

Financial Disclosure

Data:

Not applicable.

The Applicant's Position:

Details of financial disclosure are provided in Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted information for all 458 Principal Investigators and sub-investigators who participated in Study CBGJ398X2204. According to the Applicant, none of these investigators had financial information to disclose (as documented in FDA's Form 3454 included in the NDA). Fourteen investigators (or their sites) did receive total fees from QED valued between \$^{(b) (6)} and \$^{(b) (6)}. Upon review, FDA concluded that these financial interests are not likely to have had a material impact on the conduct of the CBGJ398X2204 trial.

Patient Disposition

Data:

Overall patient disposition for Study CBGJ398X2204 is presented in Table 23 below.

Table 23: Subject Disposition (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	All Subjects (N=108) n (%)
Subjects received study treatment	108 (100.0)
Subjects with treatment ongoing	12 (11.1)
Subjects ended treatment	96 (88.9)
AE	15 (13.9)
Death	1 (0.9)
Progressive Disease	67 (62.0)
Physician decision	9 (8.3)
Subject decision or withdrawal of consent	3 (2.8)
Missing	1 (0.9)

Abbreviations: AE=adverse event
Note: A subject was considered to have ended treatment if “dose permanently discontinued” was flagged on the dosing form and/or on the End of Treatment form; the date of discontinuation and/or reason was filled out.
Source: CBGJ398X2204 CSR, Table 8; adsl.xpt

The Applicant’s Position:

A total of 108 subjects received study treatment and are included in the Interim Analysis Set 2 for Cohort 1. A total of 12 subjects (11.1%) continued on study treatment as of the data cutoff; 96 subjects (88.9%) had ended treatment. Most subjects discontinued infigratinib treatment because of disease progression (62%), while 13.9% discontinued due to an AE.

The FDA’s Assessment:

FDA agrees with Applicant’s presentation of patient disposition. Upon review, the cases of “physician decision” were due to clinical progression with 2 exceptions: one patient who was discontinued from the study to pursue surgery and one patient who opted for symptomatic treatment only given the poor prognosis. Progressive disease was the cause of treatment withdrawal in 75 (69%) patients. Of the three patients who withdrew consent, the available information indicates that one withdrew to pursue treatment in her home country and one withdrew to pursue transplantation.

Protocol Violations/Deviations

Data:

Important protocol deviations are presented in Table 24 below.

Table 24: CSR Reportable Protocol Deviations (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	All Subjects (N=108) n (%)
Any CSR reportable protocol deviation	35 (32.4)
Prohibited concomitant medication	22 (20.4)
Study treatment deviation / Study drug ^a	11 (10.2)
Significant procedural deviation	5 (4.6)
Other	2 (1.9)
Selection criteria not met / Eligibility ^a	3 (2.8)
Met treatment withdrawal criteria but was not withdrawn	1 (0.9)
Abbreviations: CSR=clinical study report. Note: Subjects may be reported in multiple categories but within each category a subject was counted only once. ^a The 2 categories are synonymous; they appear separately in the source. Source: CBGJ398X2204 CSR, Table 9; adsl.xpt	

The Applicant's Position:

Overall, 35 subjects (32.4%) in the study had at least 1 CSR-reportable protocol deviation, primarily due to use of prohibited medications (22 subjects [20.4%]) and deviations related to use of study drug (11 subjects [10.2%]). Deviations related to use of study drug included, but were not limited to, failure to interrupt treatment after meeting a criterion for drug interruption, not receiving the full dose, and receiving the wrong formulation.

Deviations related to eligibility or selection criteria not met were having inorganic phosphorus outside of normal range, not receiving prior gemcitabine as required per protocol, and history of atrial fibrillation. None of the protocol deviations are considered to have a meaningful impact on the overall study outcome, and all 108 subjects who received study treatment are included in the intent-to-treat Interim Analysis Set 2 for Cohort 1.

The FDA's Assessment:

FDA reviewed data for the 35 patients summarized in Table 24 who had at least one reportable protocol deviation. Events of using prohibited medications included the use of QT-prolonging medications (such as fentanyl, ondansetron, azithromycin, amiodarone, citalopram, escitalopram), calcium supplementation, and vitamin D supplementation. Study treatment/study drug deviations included not receiving the full dose of study drug, not temporarily holding drug despite the occurrence of toxicity for which holding infigratinib was recommended, and two patients receiving the "incorrect" FMI formulation. Procedural deviations included events related to signing informed consent forms (including revised forms), obtaining pregnancy tests as scheduled, and missing end-of-treatment/safety follow-up visits. The deviations related to selection criteria/eligibility (3 events) and "other" (2 events) were:

- Enrollment despite clinically-significant history of atrial fibrillation.
- Enrollment despite phosphorus level outside the normal limits.
- Enrollment despite not having received prior gemcitabine therapy.
- Incorrect washout period between gemcitabine/cisplatin and initiation of this study.
- Prior receipt of an FGFR inhibitor.

Upon requests, QED provided information on patients enrolled despite not having prior gemcitabine therapy; FDA confirmed all three patients received prior gemcitabine-based systemic therapy although the therapy was given in the neoadjuvant/adjuvant setting.

Based on the nature of these protocol deviations, with the exception of the patient with prior treatment with an FGFR inhibitor, it is unlikely that the protocol violations had an impact on the observed efficacy outcomes of the study. Prior treatment with an FGFR inhibitor may have resulted in resistance to inhibition of the pathway and therefore inclusion of this patient would not be expected to bias results towards success. All other protocol violations may have had an impact on tolerability of the drug or increase the risk of a particular patients, but did not interfere with the assessment of the safety of infigratinib. The reported protocol deviations/violations do not appear to be a significant cause of bias influencing the study results

Demographic and Baseline Characteristics

Data:

Subject demographics and baseline characteristics are presented in Table 25 below.

Table 25: Subject Demographics and Baseline Disease Characteristics (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	All Subjects (N=108)
Region – n (%)	
Western Europe	24 (22.2)
North America	77 (71.3)
Asia	7 (6.5)
Race – n (%)	
White	78 (72.2)
Black or African American	4 (3.7)
Asian	11 (10.2)
Other/Unknown	15 (13.9)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	All Subjects (N=108)
Age (Years)	
Mean (SD)	53.4 (13.08)
Median	53.0
Min, max	23, 81
Age group – n (%)	
18 to <65 years	82 (75.9)
65 to <85 years	26 (24.1)
≥85 years	0
Sex – n (%)	
Male	41 (38.0)
Female	67 (62.0)
BMI (kg/m²)	
n	102
Mean (SD)	26.4 (6.64)
Median	25.5
Min, max	16.0, 50.6
ECOG PS, n (%)	
0	45 (41.7)
1	62 (57.4)
2	1 (0.9)
Primary site of cancer, n (%)	
Bile Duct	106 (98.1)
Cholangiocarcinoma	1 (0.9)
Liver	1 (0.9)
Non-liver metastatic status, n (%)	
No metastatic site	5 (4.6)
Had metastatic site(s)	102 (94.4)
Bone	28 (25.9)
Lung	74 (68.5)
Node	62 (57.4)
Other	41 (38.0)
Time from initial diagnosis to first dose day (months)	
N	108
Mean (SD)	21.73 (24.77)
Median	12.75
Min, max	1.74, 152.94
Time from the most recent recurrence/progression to the first dose day (months)	
N	98

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	All Subjects (N=108)
Mean (SD)	2.20 (2.71)
Median	1.40
Min, max	0.03, 14.59
Histological grade, n (%)	
Well differentiated	9 (8.3)
Moderately differentiated	42 (38.9)
Poorly differentiated	33 (30.6)
Undifferentiated	1 (0.9)
Unknown/missing	22 (20.4)
Not applicable	1 (0.9)
Stage at time of study entry, n (%)	
Stage II	1 (0.9)
Stage III	0
Stage IV	107 (99.1)
Prior Therapies	
≤1	50 (46.3)
>1	58 (53.7)
Gemcitabine-based Therapy	
Intolerant	13 (12.0)
Progressed	95 (88.0)
Abbreviations: BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; PS=performance status; SD=standard deviation. Source: CBGJ398X2204 CSR, Tables 11, 12, 13; adsl.xpt	

The Applicant's Position:

Subjects were enrolled in North America (71.3%), Western Europe (22.2%), or Asia (6.5%). Most subjects were white (72.2%) and most were female (62.0%). Mean age of the study population was 53.4 years (range: 23 to 81 years); 82 subjects (75.9%) were <65 years of age.

All but 1 subject had a baseline ECOG PS of 0 (41.7%) or 1 (57.4%). The bile duct was the primary site of cancer in most subjects (98.1%). Nearly all (94.4%) of the subjects had non-liver metastatic disease at baseline; the most common metastatic sites were the lung (68.5%) and lymph nodes (57.4%). Histological grade was typically characterized as moderately differentiated (38.9%), poorly differentiated (30.6%), unknown/missing (20.4%), or well differentiated (8.3%). At initial diagnosis, the most common cancer stage was Stage IV (70.4%). Nearly all subjects had Stage IV disease at study entry (99.1%), with 1 subject (0.9%) having Stage II disease.

Median time from initial diagnosis to first infigratinib dose was 12.75 months (range: 1.74 to

152.94 months) and median time from the most recent recurrence/progression to first infigratinib dose was 1.40 months (range: 0.03 to 14.59 months). The majority of subjects (96.3%) had progressed on >1 prior regimen.

Overall, the demographics, baseline characteristics, and prior treatment of subjects enrolled in CBGJ398X2204 are representative of this refractory patient population and standard of treatment for cholangiocarcinoma. The predominantly younger and female population is also consistent with existing scientific literature describing patients with FGFR2 fusion positive cholangiocarcinoma.

The FDA's Assessment:

FDA agrees with Applicant's summary of main demographic and baseline disease characteristics. No data on ethnicity was provided. Although the population may slightly differ from the general U.S. CCA population, it appears consistent with the subset of patients with FGFR2 altered CCA: majority of patients were woman (63%), White (72%), and younger than 65 years of age (76%). As noted above in Section 2.1, overall the CCA population in the US is White (78%), older than 65 years of age (63%), and 49% of patients are woman. African Americans accrual of 4% is less than a third of the expected 14% African American contribution to the U.S. population based on 2019 U.S. Census. The patient population in Study CBGJ398X2204 appears to be representative of the intended treatment population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

A summary of treatment compliance observed on Study CBGJ398X2204 is provided in the table below.

Table 26: Treatment Compliance (Study CBGJ398X2204)

Relative dose intensity ^a	Total
Interim Analysis Set 2 for Cohort 1, n	108
Mean (SD), %	77.9 (17.58)
Categories, n (%)	
≤50%	4 (3.7)
50% to ≤75%	44 (40.7)
>75% to ≤90%	24 (22.2)
>90% to ≤100	30 (27.8)
>100%	6 (5.6)
Sensitivity Analysis Set for Cohort 1, n	100
Mean (SD), %	77.4 (17.81)
Categories, n (%)	
≤50%	4 (4.0)
50% to ≤75%	42 (42.0)
>75% to ≤90%	21 (21.0)
>90% to ≤100	28 (28.0)
>100%	5 (5.0)
Abbreviations: SD=standard deviation.	
^a Relative dose intensity = Actual cumulative dose (mg) / Planned cumulative dose (mg) within the actual treatment duration.	
Source: CBGJ398X2240 CSR, Table 17; adsl.xpt	

A summary of concomitant medication use observed on Study CBGJ398X2204 is provided in Table 27 and Table 28 below.

Table 27: ATC Classes of Concomitant Conditions Taken by ≥15% of All Subjects (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

ATC Class	All Subjects (N=108) n (%)
Any concomitant medication	107 (99.1)
Drugs for treatment of hyperkalemia and hyperphosphatemia	84 (77.8)
Natural opium alkaloids	49 (45.4)
Benzodiazepine derivatives	48 (44.4)
Proton pump inhibitors	44 (40.7)
Other antiemetics	40 (37.0)
Osmotically acting laxatives	39 (36.1)
Contact laxatives	38 (35.2)
Other ophthalmologicals	37 (34.3)
Glucocorticoids	32 (29.6)
Other agents for local oral treatment	31 (28.7)
Serotonin (5HT3) antagonists	29 (26.9)
Electrolyte solutions	28 (25.9)
Heparin group	25 (23.1)
Softeners, emollients	24 (22.2)
Anilides	23 (21.3)
Propionic acid derivatives	23 (21.3)
Bisphosphonates	21 (19.4)
Fluoroquinolones	21 (19.4)
Propulsives	18 (16.7)
Other analgesics and antipyretics	17 (15.7)
Abbreviations: ATC=Anatomical Therapeutic Class. Note: Terms are sorted in descending frequency for the All Subjects column and then alphabetically for like frequency. Source: CBGJ398X2204 CSR, Table 15; adsl.xpt, adae.xpt	

Table 28: Summary of Phosphate-binders (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	All Subjects (N=108) n (%)
Subjects Taking phosphate-binder medication	
No	21 (19.4)
Yes	87 (80.6)
Subjects who had hypophosphatemia AE ^a	23 (26.4)
Grade 1	5 (5.7)
Grade 2	4 (4.6)
Grade 3	13 (14.9)
Grade 4	1 (1.1)
Name of phosphate-binder taken, n (%)	
Sevelamer	60 (55.6)
Sevelamer hydrochloride	15 (13.9)
Sevelamer carbonate	9 (8.3)
Calcium carbonate	5 (4.6)
Calcium polystyrene sulfonate	2 (1.9)
Lanthanum carbonate	2 (1.9)
Sucroferric oxyhydroxide	1 (0.9)
Abbreviations: AE=adverse event. Note: Names of phosphate binders are sorted in descending frequency for the All Subjects column and then alphabetically for like frequency. ^a Only includes subjects who took ≥1 phosphate-binder medication. The denominator was subjects who took ≥1 phosphate-binder medication. Hypophosphatemia includes both hypophosphatemia and blood phosphorus decrease. Source: CBGJ398X2204 CSR, Table 16; adlb.xpt	

The Applicant's Position:

The mean treatment compliance among subjects was 77.9%. 107 subjects (99.1%) took at least 1 concomitant medication during the study. The most common ATC classes of concomitant medication were drugs for treatment of hyperkalemia and hyperphosphatemia (77.8%), natural opium alkaloids (45.4%), benzodiazepine derivatives (44.4%), proton pump inhibitors (40.7%), and other antiemetics (37.0%). The most common concomitant medications (by PT) were sevelamer (60 subjects [55.6%]), lorazepam (30 subjects [27.8%]), prochlorperazine (29 subjects [26.9%]), ondansetron (26 subjects [24.1%]), oxycodone (25 subjects [23.1%]), sodium chloride (24 subjects [22.2%]), and paracetamol (23 subjects [21.3%]).

Phosphate-lowering treatment with low phosphate diet and phosphate binding therapy (eg, sevelamer hydrochloride) were used from the initiation of study treatment and for management of hyperphosphatemia. 87 subjects (80.6%) took a phosphate-binding medication during the study. Of these, 23 subjects (26.4%) had hypophosphatemia reported as a TEAE, with 13 subjects (14.9%) having Grade 3 hypophosphatemia and 1 subject (1.1%) having Grade 4

hypophosphatemia. The most common phosphate-binding medications (by PT) were sevelamer (55.6%), sevelamer hydrochloride (13.9%), and sevelamer carbonate (8.3%).

The FDA's Assessment:

The Applicant describes the relative dose intensity, concomitant medications, and the use of phosphate binders above. Based on these data, approximately 55% of patients received >75% of planned doses. As stated in Section 6, FDA does not agree that the dosage used in Study CBGJ398X2204 has been optimized for safety and efficacy, and 60% and 69% patients required infigratinib dose reductions or treatment interruptions to manage toxicities. Regarding concomitant medications, the ATC classes of medications used concomitantly by patients in Study CBGJ398X2204 are generally reflective of medications often used in the oncology setting with the exception of phosphate binders.

Approximately 81% (87/108) of patients on Study CBGJ398X2204 used a phosphate binder at some point during treatment to address increased phosphate serum levels, a class effect that FGFR inhibitors have on mineral metabolism. The analysis of the need for and impact of phosphate binders intake in patients taking infigratinib is confounded by the fact that Study CBGJ398X2204 initially required the prophylactic use of phosphate-binders. The protocol was later revised so that phosphate binders were only required if serum phosphate levels were elevated > 5.5 mg/dL. Based on information provided in response to an information request by FDA, the Applicant stated that 52 (48%) patients initiated a phosphate binder prophylactically and 21 (19%) patients initiated a phosphate-binder after having a serum phosphate level > 5.5 mg/dL. The remaining 21 patients (out of 108) did not receive any phosphate binders while on-study. Additional information on phosphate binders administration, hyper-, and hypophosphatemia can be found on the Sections 8.2.5 and 6.2.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

A summary of primary efficacy results for ORR assessed by BICR is presented in Table 29 below. The subgroup analyses of overall response rate assessed by BICR is presented in Figure 9 below.

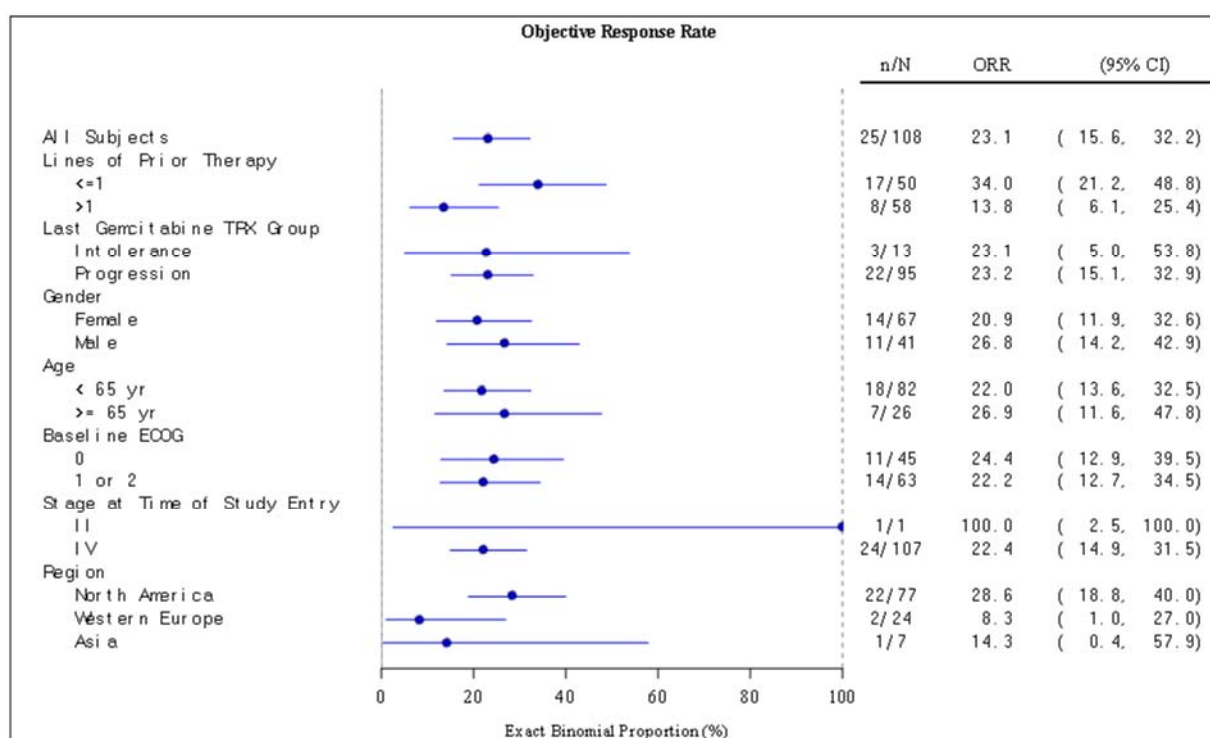
Table 29: Primary Endpoint of Overall Response Rate Assessed by BICR (Study CBGJ398X2204)

PRIMARY ENDPOINT	Total
Overall Response Rate ^a by BICR	
Interim Analysis Set 2 for Cohort 1, n	108
n (%)	25 (23.1)
95% CI ^b	15.6, 32.2

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Sensitivity Analysis Set for Cohort 1, n	100
n (%)	23 (23.0)
95% CI ^b	15.2, 32.5
Abbreviations: BICR=blinded independent central review; CI=confidence interval; CR=complete response; PR=partial response.	
^a Proportion with a best overall response of confirmed CR or PR.	
^b Binomial proportion with exact 95% CI.	
Source: CBGJ398X2204 CSR, Table 18; adsl.xpt, adef.xpt	

Figure 9: Subgroup Analyses of Overall Response Rate Assessed by BICR (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)



Abbreviations: BICR=blinded independent central review; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ORR=overall response rate; TRX=treatment; yr=year.
Source: CBGJ398X2204 CSR, Figure 8

The Applicant's Position:

Infigratinib showed a clinically meaningful response rate in this population. The primary endpoint (ORR assessed by BICR among subjects in the Interim Analysis Set 2 for Cohort 1) was 23.1% (95% confidence interval [CI]: 15.6, 32.2) including 1 subject with confirmed CR and 24 subjects with confirmed PR. The 95% CI based on the binomial distribution (Clopper-Pearson exact method) excluded 15% as the lower bound of the CI, supporting robust antitumor activity

for this single-agent, oral, targeted therapy. Similar to the BICR assessment of efficacy, the secondary endpoint of ORR assessed by the investigator was 30.6% (95% CI: 22.1, 40.2), with a median DOR of 5.95 months (range: 0.95+, 19.12). A total of 12 subjects (36.4%) had DOR $\geq$ 6 months, 6 subjects (18.2%) had DOR $\geq$ 9 months, and 1 subject (3.0%) had DOR $\geq$ 12 months.

All subgroups appeared to derive benefit for the efficacy endpoints analyzed. Moreover, the magnitude of ORR benefit assessed by BICR among subjects who received infigratinib in the true second-line setting (34.0%, 17/50, 95% CI: 21.2, 48.8) and in the third- or later-line therapy setting (13.8%, 8/58, 95% CI: 6.1, 25.4) is clinically meaningful. Notably, the third- or later-line therapy subgroup is heterogeneous, encompassing patients who received 2 to 8 prior lines of treatment. Durable responses in this more refractory subgroup further support meaningful clinical activity in this population.

Similar results were seen in the Sensitivity Analysis Set. These primary results are especially meaningful since >99% of subjects treated with infigratinib had Stage IV cancer at study enrollment, 99% had received a prior gemcitabine-based regimen, and 54% had received 2 or more prior lines of therapy.

The FDA's Assessment:

FDA agrees with the applicant's presentation of the efficacy results based on overall response rate (ORR) accompanied by durability of response (DOR). According to BICR, the ORR was 23.1% (95% CI: 15.6%, 32.2%) with a median DOR of 5.03 months (95% CI: 3.71, 9.26). The following table provides a summary of FDA's analysis of ORR and DOR according to BICR and investigator assessment.

Table 30: ORR and DOR results by BICR and Investigator Assessment (N = 108)

	BICR	Investigator Assessed
ORR (95% CI)	23.1% (15.6%, 32.2%)	30.6% (22.1, 40.2)
CR	1	0
PR	24	33
Median DOR (95% CI)	5.03 (3.71, 9.26)	5.95 (5.16, 9.00)
Range (months)	(0.92+, 19.1)	(0.95+, 19.1)
DOR $\geq$ 6 months	8 (32%)	12 (36.4%)
DOR $\geq$ 12 months	1 (4%)	1 (3%)

The concordance between BICR and Investigator assessment was 80%. The following table shows the concordance between BICR and investigator assessment. Among 25 responders by BICR, 18 were assessed as responders by the investigator.

Table 31: Concordance between BICR and Investigator assessed ORR

BICR	Investigator Assessment		Totals
	Response	Non-Response	
Response	18 (16.7%)	7 (6.5%)	25 (23.1%)
Non-Response	15 (13.9%)	68 (63%)	83 (76.9%)
Totals	33 (30.6%)	75 (69.4%)	108 (100%)

Although the response rate can be considered modest, FDA agrees that the magnitude of effect of infigratinib, in the context of a high unmet need, and based on durability of the responses, is clinically meaningful. FDA disagrees with several of the Applicant's statements; it is unclear why exclusion of a 15% lower bound of the CI for the ORR would be supportive of a robust effect and the review team notes that the lower bound of the 95% CI for infigratinib ORR is 15.6%. FDA does not consider inferential procedures in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response, compared with the available therapies at the time of approval.

Further, FDA acknowledges that the exploratory subgroup analyses, although limited by small sample size, appear to support a consistent effect of infigratinib across subgroups; however, FDA cautions that results in subgroups are limited by small sample sizes and wide confidence intervals.

In addition to the exploratory subgroup analyses performed by the Applicant, FDA conducted exploratory subgroup analyses of response by FGFR2 alteration type which, although limited by small sample size, also appear to show consistent results. The ORR was 23.9% (95% CI: 15.4, 34.1) in patients with tumors having FGFR2 fusions (n=88) and 22.2% (95% CI: 6.4, 47.6) in patients with tumors having other rearrangements (n=18). There were no responses in two patients whose tumors had unknown status (whether a fusion of other rearrangement). See Appendix 19.4.5 for more details.

FDA considers the analysis in the Sensitivity Analysis Set to be exploratory.

Data Quality and Integrity

Data:

Not applicable.

The Applicant's Position:

No data integrity concerns were reported.

The FDA's Assessment:

No significant data integrity concerns were noted.

Efficacy Results – Secondary and other relevant endpoints

Data:

Results for the secondary endpoints are presented in Table 32, Table 33, Table 34 and Figure 10 below.

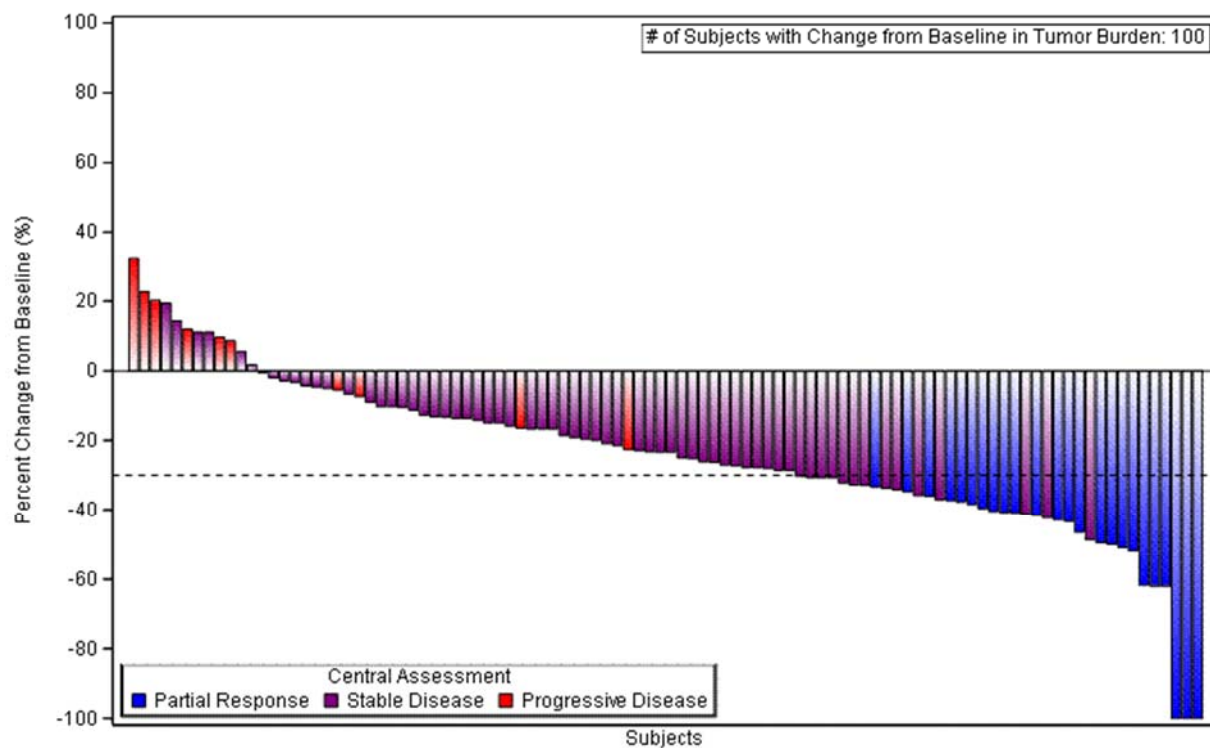
Table 32: Summary of Efficacy Results by BICR and Investigator (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	Assessment of Disease	
	BICR	Investigator
Secondary Endpoints, n	108	108
Overall response rate ^a, n (%)	Primary Objective (Table 29)	33 (30.6)
(95% CI) ^b		(22.1, 40.2)
Duration of response ^c, n	25	33
Kaplan-Meier estimate		
Median, months	5.03	5.95
95% CI	3.71, 9.26	5.16, 9.00
Min, max, months	0.92+, 19.12	0.95+, 19.12
≥12 months, n (%)	1 (4.0)	1 (3.0)
≥9 to <12 months, n (%)	3 (12.0)	5 (15.2)
≥6 to <9 months, n (%)	4 (16.0)	6 (18.2)
Response onset		
Mean (standard deviation), months	3.21 (1.71)	3.58 (3.29)
Median, months	3.61	1.91
(Min, max), months	(1.38, 7.36)	(1.38, 18.76)
Best overall response, n	108	108
Confirmed CR, n (%)	1 (0.9)	0
Confirmed PR, n (%)	24 (22.2)	33 (30.6)
Stable disease ^d , n (%)	66 (61.1)	58 (53.7)
Progressive disease, n (%)	11 (10.2)	11 (10.2)
Not Done, n (%)	6 (5.6)	6 (5.6)
Disease control rate ^e, n	108	108
Event, n (%)	91 (84.3)	91 (84.3)
(95% CI) ^b	(76.0, 90.6)	(76.0, 90.6)
Progression-free survival ^f, n	108	108
Event, n (%)	73 (67.6)	76 (70.4)
Median, months	7.29	6.77
(95% CI)	(5.59, 7.56)	(5.55, 7.56)
Overall survival		108
Death event, n (%)	NA	70 (64.8)
Median, months		12.16

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

	Assessment of Disease	
	BICR	Investigator
Secondary Endpoints, n	108	108
(95% CI) ^b		(10.68, 14.85)
BICR=blinded independent central review; CI=confidence interval; CR=complete response; max=maximum; min=minimum; NA=not applicable; PR=partial response. + indicates numbers reported for subjects whose response is still ongoing. ^a Proportion with a best overall response of confirmed CR or PR. ^b Binomial proportion with exact 95% CI. ^c Duration of response calculated as months from initial response to disease progression or death due to any cause in confirmed responders. ^d Non-CR/nonprogressive disease considered stable disease for subjects who only have non-target lesions at baseline. ^e Subjects with best overall response as confirmed CR, PR, or stable disease (including unconfirmed CR/PR). ^f Progression-free survival was calculated as the number of months from the first dose of study drug to progression or death due to any cause, whichever occurred earlier. Subjects without an assessment of progression or death were censored at the last adequate tumor assessment. For subjects who had an event after ≥2 missed visits, the subject was censored at the last adequate tumor assessment before the missing visit. Source: 2.5 Clinical Overview, Table 2; adsl.xpt, adef.xpt, adtte.xpt		

Figure 10: Waterfall Plot of Maximum Percent Reduction in Tumor Burden with Best Response Assessment by BICR (CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)



Abbreviation: BICR=blinded independent central review.

Note: The colors of the bars are based on confirmed response per blinded central assessment.

Source: CBGJ398X2204, Figure 2

Table 33: Secondary Endpoint of Progression-free Survival (Study CBGJ398X2204 Interim Analysis Set 2)

Progression-Free Survival	Total
By BICR, n	108
Subjects with events, n (%)	73 (67.6)
Disease progression, n (%)	63 (58.3)
Death, n (%)	10 (9.3)
Censored, n (%)	35 (32.4)
Time to event, months	
Median	7.29
95% CI	5.59, 7.56
Min, max	0.03+, 20.90
Kaplan-Meier Estimate	
4 months, % (95% CI)	75.2 (65.2, 82.7)
6 months, % (95% CI)	56.6 (45.5, 66.3)
8 months, % (95% CI)	33.1 (22.9, 43.7)
12 months, % (95% CI)	17.1 (9.2, 27.0)
18 months, % (95% CI)	2.5 (0.2, 10.9)
By Investigator, n	108
Subjects with events, n (%)	76 (70.4)
Disease progression, n (%)	72 (66.7)
Death, n (%)	4 (3.7)
Censored, n (%)	32 (29.6)
Time to event, months	
Median	6.77
95% CI	(5.55, 7.56)
Min, max	0.03+, 26.35+
Kaplan-Meier Estimate	
4 months, % (95% CI)	72.1 (62.0, 80.0)
6 months, % (95% CI)	55.7 (44.8, 65.2)
8 months, % (95% CI)	32.3 (22.4, 42.5)
12 months, % (95% CI)	21.3 (12.9, 31.0)
18 months, % (95% CI)	4.5 (0.9, 13.0)
24 months, % (95% CI)	2.3 (0.2, 10.0)
Abbreviations: BICR=blinded independent central review. + indicates censoring. Note: Progression-free survival was calculated as the number of months from the first dose of study drug to progression or death due to any cause, whichever occurred earlier. Subjects without an assessment of progression or death were censored at the last adequate tumor assessment. For subjects who had an event after ≥2 missed visits, the subject was censored at the last adequate tumor assessment before the missing visit. Source: CBGJ398X2204 CSR, Table 19; adsl.xpt, adtte.xpt	

Table 34: Overall Survival (Study CBGJ398X2204)

Overall Survival	Total
Interim Analysis Set 2 for Cohort 1, n	108
Death: n (%)	70 (64.8)
Censored: n (%)	38 (35.2)
Time to Event (months)	
Median	12.16
95% CI (median)	10.68, 14.85
Min, max	1.15, 55.89+
Sensitivity Analysis Set for Cohort 1, n	100
Death: n (%)	70 (70.0)
Censored: n (%)	30 (30.0)
Time to Event (months)	
Median	12.16
95% CI (median)	10.58, 14.85
Min, max	1.15, 55.89+
Abbreviations: CI=confidence interval + indicates censoring. Note: Overall survival was calculated as the number of months from the date of the first dose of the study drug to the death date due to any cause. Subjects without death recorded were censored at the last known to be alive date. Source: CBGJ398X2204 CSR, Table 21; adsl.xpt, adtte.xpt	

The Applicant's Position:

Results from all secondary efficacy endpoints were consistent with and supportive of results from the primary efficacy analysis:

- ORR assessed by the investigator was 30.6% (95% CI: 22.1, 40.2), with a median DOR of 5.95 months (95% CI: 5.16, 9.00; range: 0.95-19.12 months).
- BOR assessed by BICR was confirmed CR (0.9%), confirmed PR (22.2%), stable disease (61.1%) and progressive disease (10.2%).
 - o 1 subject had confirmed CR by BICR.
 - o 2 additional subjects had unconfirmed CRs by BICR; 1 subject proceeded to a planned resection of metastatic lesion and discontinued study treatment before confirmation and 1 subject had confirmed PR followed by CR and remains on the study as of the data cutoff.
 - o Within the 66 subjects (61.1%) with stable disease, 12 subjects (11.1%) had a response of unconfirmed CR/PR. All 12 subjects with unconfirmed response have discontinued as of the data cutoff of 31 Mar 2020. Of these 12 subjects, 9 subjects discontinued for disease progression per investigator's assessment, 2 subjects discontinued for adverse events, and 1 subject discontinued for physician decision

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

- BOR assessed by the investigator was confirmed CR (0%), confirmed PR (30.6%), stable disease (53.7%) and progressive disease (10.2%).
- DCR assessed by BICR was 84.3% (95% CI: 76.0, 90.6). DCR assessed by the investigator was 84.3% (95% CI: 76.0, 90.6).
- Disease progression assessed by BICR or death occurred in 67.6% of subjects and the median PFS was 7.29 months (95% CI: 5.59, 7.56). Disease progression assessed by the investigator or death occurred in 70.4% of subjects and the median PFS was 6.77 months (95% CI: 5.55, 7.56).
- Median OS was 12.16 months (95% CI: 10.68, 14.85); 64.8% of subjects died.

Results assessed by the investigator were similar to those from BICR.

Infigratinib showed a clinically relevant magnitude and duration of benefit in subjects with advanced or metastatic cholangiocarcinoma. These results are especially meaningful since approximately 99.1% of all subjects enrolled had Stage IV cancer (including 68.5% with lung metastases) and most subjects (54%) were heavily pretreated and receiving infigratinib as third- or later-line therapy. This refractory population represents a significant unmet medical need of patients who have limited effective therapeutic options available.

The FDA's Assessment:

FDA agrees with the results presented for ORR and DOR by investigator. Refer to FDA's assessment of concordance between BICR and investigator in the Efficacy Results – Primary Endpoint subsection (Table 31).

FDA also agrees with the BOR results presented by BICR and investigator and considers this information to be descriptive in support of the respective ORR results. FDA acknowledges that there were 12 patients with unconfirmed responses, but the primary endpoint was ORR as per RECIST 1.1, which mandates confirmation of the response in a subsequent scan and therefore unconfirmed responses do not inform the outcomes of the study. FDA's evaluation of the primary endpoint of ORR by BICR only focused on patients with confirmed response.

FDA considers time-to-event endpoints like PFS and OS to be uninterpretable in a single-arm study. The analyses of PFS and OS in study CBGJ398X2204 are considered exploratory and the results descriptive, therefore FDA did not verify them. Also, analyses of DCR are exploratory and FDA did not verify the results.

Dose/Dose Response

Data:

Not Applicable.

The Applicant's Position:

Dose-response relations were not studied in this trial. Please see Section 6.2.2.1 above.

The FDA's Assessment:

N/A

Durability of Response

Data:

Of the 25 subjects who achieved a confirmed CR or confirmed PR by BICR, 8 subjects (32%) had a response duration ≥ 6 months. 4 subjects (16.0%) had DOR ≥ 9 months, and 1 subject (4.0%) had DOR ≥ 12 months (max: 19 months).

The Applicant's Position:

DOR ≥ 6 months in 32% of responders supports meaningful clinical benefit in patients with cholangiocarcinoma who have received prior treatment, given that the life expectancy in this setting is 5-7 months.

The FDA's Assessment:

Refer to FDA's assessment of DOR in the Efficacy Results – Primary Endpoint subsection (Table 30). Although FDA agrees that an ORR of 23.1% (95% CI: 15.6%, 32.2%) with a median DOR of 5.03 months (95% CI: 3.71, 9.26) in the context of a high unmet medical need represent a clinical benefit, the review team disagrees with the Applicant statement above. Only 8 patients in Study 2204 had a response lasting more than 6 months, which further support the need for a subsequent study to confirm the clinical benefit of infigratinib in patients with cholangiocarcinoma harboring FGFR2 gene fusions or rearrangements.

Persistence of Effect

Data:

Time to event endpoints were assessed as secondary endpoints to further characterize the clinical benefit of infigratinib in patients with previously treated cholangiocarcinoma and FGFR2 fusions receiving infigratinib. The median PFS of 7.29 months (95% CI: 5.59, 7.56) by BICR and median OS of 12.16 months are consistent with the primary endpoint of ORR supported by duration of response, and further support that infigratinib provides a clinically relevant duration of benefit.

The Applicant's Position:

No controlled studies were conducted that were specifically designed to collect long-term efficacy data.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

The FDA's Assessment:

FDA reiterates that time-to-event endpoints like PFS and OS are uninterpretable in a single-arm study in the absence of a comparator arm. Thus, these results should not be considered in the assessment of persistence of effect.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

Additional Analyses Conducted on the Individual Trial

Data:

A summary of the PK assessment is presented in Table 35 below.

Table 35: PK Assessment (Study CBGJ398X2204)

	Cycle 1 Day 1 Mean (%CV)					
PK Parameter	n	Infigratinib	n	BHS697	n	CQM157
AUC ₀₋₂₄ (h*ng/mL)	14	1397.3 (57.0)	15	221.3 (62.5)	3	950.4 (75.9)
C _{max} (ng/mL)	18	151.4 (68.3)	17	15.02 (69.3)	18	40.81 (64.5)
T _{max} (h) ^a	18	3.00 (1.87-7.08)	17	3.00 (2.00-23.7)	18	8.00 (5.63-25.75)
T _{1/2} (h) ^a	8	6.33 (4.20, 7.78)	--	NC	--	NC
	Cycle 1 Day 15 Mean (%CV)					
AUC ₀₋₂₄ (h*ng/mL)	7	6084.5 (45.7)	7	1105.6 (54.9)	6	466.8 (55.8)
C _{max} (ng/mL)	10	332 (50.8)	10	54.86 (59.4)	10	21.12 (75.5)
T _{max} (h) ^a	10	4.63 (2.05-7.12)	10	4.00 (2.97-24.00)	10	5.13 (0.40-24.00)
T _{1/2} (h) ^a	--	NC	--	NC	--	NC
AR AUC ₀₋₂₄	5	4.97 (43.6)	5	7.37 (41.8)	1	0.5080 (NC)
M:P AUC ₀₋₂₄	--	NA	7	0.198 (41.3)	4	0.146 (87.1)
M:P=metabolite to parent ratio; NC=not calculated; NA=not applicable; RACC=accumulations ratio AUC ₀₋₂₄ , Day 15 / AUC ₀₋₂₄ Day 1						
^a T _{max} and T _{1/2} are reported as median (min, max)						
Note: This table only includes data for patients who received FMI III						
Source: CBGJ398X2204 CSR, Table 26; adlb.xpt						

The Applicant's Position:

PK assessment of intensive sampling results on Day 1 and Day 15 showed significant accumulation of infigratinib (5 fold) and the BHS697 metabolite (7-fold) on Day 15 compared with Day 1 in terms of AUC_{0-24} , consistent with the predose concentrations from sparse sampling. Exposure of the CQM157 metabolite in terms of AUC_{0-24} decreased by approximately 50% on Day 15 relative to Day 1. The metabolite to parent ratio was similar between Day 1 and Day 15 for BHS697, but lower on Day 15 compared with Day 1 for CQM157. At steady state (Day 15), the BHS697 metabolite represented 20% of infigratinib exposure and the CQM157 metabolite represented 15% of infigratinib exposure in plasma. The CL/F and apparent volume of distribution for infigratinib decreased on Day 15 compared with Day 1. PK was assessed from intensive and sparse sampling. Predose concentrations of infigratinib and BHS697 increased from C1D2 to C1D15 and remained constant or decreased on C1D21, whereas predose concentration of CQM157 remained constant during this period.

The FDA's Assessment:

FDA generally agrees with the Applicant that the PK properties of infigratinib and its active metabolites (BHS697 and CQM157) were adequately characterized. See Section 6.3.1 for FDA's detailed assessment of the PK parameters for infigratinib, BHS697, and CQM157 following noncompartmental analysis (NCA) versus population PK modeling.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

FDA independent analysis of the efficacy results of Study CBGJ398X2204 in general concurs with the Applicant's analyses of the primary endpoints of ORR and DOR. There were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for patients in Cohort 1 with FGFR2 gene fusions who received at least one dose of infigratinib (Cohort 1 Interim Analysis Set 2) in Study CBGJ398X2204. The study showed a ORR of 23.1% (95% CI: 15.6%, 32.2%) as assessed by BICR according to RECIST v1.1. in FDA's primary analysis population of patients with FGFR2 gene fusions who received at least one dose of infigratinib. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Although PFS and OS results were summarized, FDA notes that time-to-event endpoints are uninterpretable without a comparator arm. PROs data were not collected in Study CBGJ398X2204.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Not Applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

Secondary and Other Endpoints

Data:

Not Applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

Subpopulations

Data:

Not Applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

Additional Efficacy Considerations

The FDA's Assessment:

N/A

8.1.5. Integrated Assessment of Effectiveness

Data:

In addition to results of Study CBGJ398X2204, brief efficacy data are provided for 4 subjects with biliary tract cancer harboring FGFR2 gene fusions in studies CBGJ398X2101 and CBGJ398XUS04:

- CBGJ398X2101 one subject with primary gallbladder cancer, received the 125 mg

3 weeks on/1 week off treatment regimen, with 1 prior line of anticancer treatment. The subject received infigratinib for 141 days and discontinued treatment due to an AE. The BOR was stable disease.

- CBGJ398X2101 one subject with primary gallbladder cancer, received the 125 mg 3 weeks on/1 week off treatment regimen, with 1 prior line of anticancer treatment. The subject received infigratinib for 910 days. The BOR was confirmed PR with a DOR of 17.5 months.
- CBGJ398X2101 one subject with primary intrahepatic cholangiocarcinoma, received the 125 mg/day continuous dosing regimen, with 1 prior line of anticancer treatment. The subject received infigratinib for 81 days and discontinued due to progressive disease. The BOR was stable disease.
- CBGJ398XUS04 one subject with primary cholangiocarcinoma with primary lesion location in the liver, received the 125 mg 3 weeks on/1 week off treatment regimen, with 2 prior lines of anticancer treatment. The subject received infigratinib for 367 days with no dose modifications. The subject discontinued for progressive disease. The BOR was stable disease.

The Applicant's Position:

These subjects are not integrated with data from study CBGJ398X2204 because studies CBGJ398X2101 and CBGJ398XUS04 had different endpoints and/or study designs. In addition, central assessments were not conducted for these 4 subjects.

One patient experienced a partial response and remained on infigratinib for 30 months. The remaining 3 subjects had stable disease as best response, one of whom remained on treatment for 1 year.

The FDA's Assessment:

Though comparisons across trials are limited, the results from the four patients, above appear consistent with the conclusions noted in Section 8.1.3.

8.2. Review of Safety

The Applicant's Position:

The clinical development program that contributed to the safety analysis for this marketing application comprises of 17 clinical studies, with 797 subjects exposed to at least one dose of infigratinib (Figure 11).

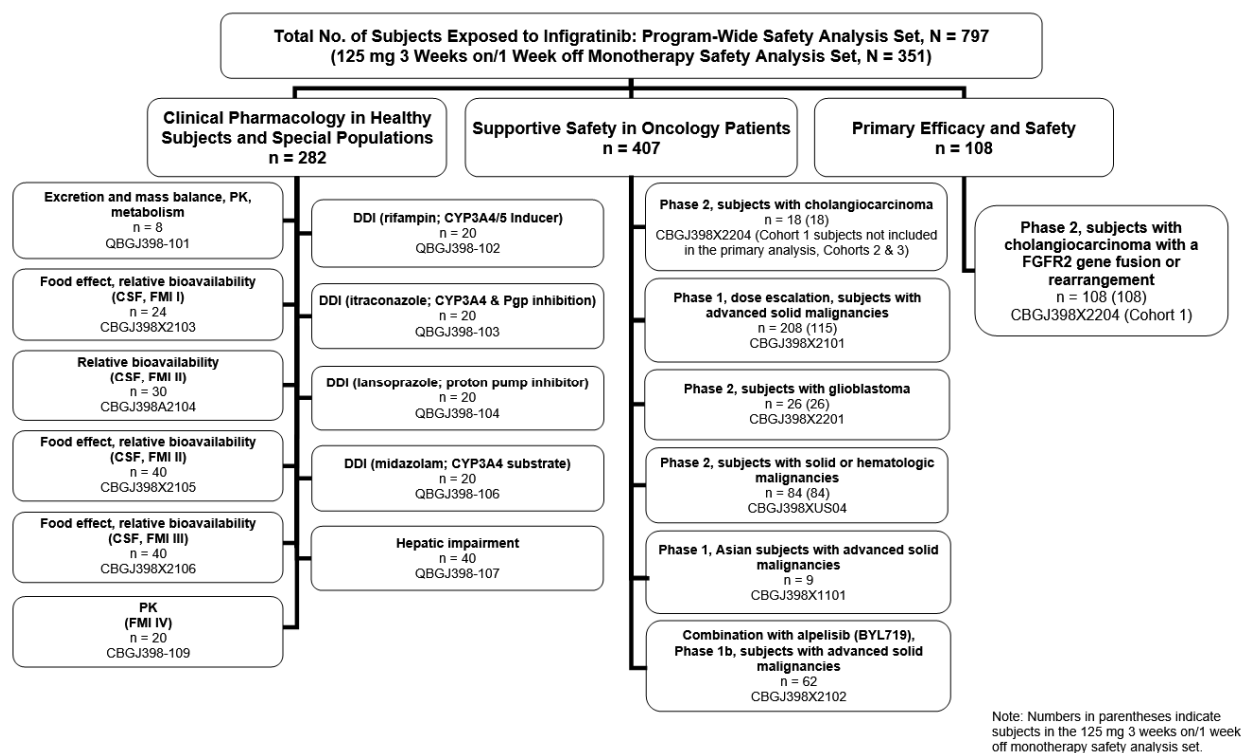
The safety evaluation focused on data from the primary safety analysis set (108 subjects from study CBGJ398X2204) and the 125 mg 3 weeks on/1 week off schedule monotherapy safety

NDA 214622 Multi-disciplinary Review and Evaluation Infigratinib (Truseltiq)

analysis set (351 subjects from studies CBGJ398X2101, CBGJ398X2201, CBGJ398X2204, and CBGJ398XUS04). In both analysis sets, subjects received infigratinib monotherapy on the 125 mg 3 weeks on/1 week off schedule. Where appropriate, program-wide safety analyses were performed (N=797 subjects); these subjects received at least one dose of infigratinib in all sponsor-initiated clinical studies.

Data from these studies allow for an informed assessment of the safety profile of infigratinib and an evaluation of the overall benefit-risk in subjects with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations. This safety population was considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

Figure 11: Number of Subjects Exposed to Infigratinib in This Safety Evaluation



The FDA's Assessment:

FDA notes the studies above and that the primary safety analysis for this application is based on the 108 patients from Cohort 1 of Study CBGJ398X2204.

8.2.1. Safety Review Approach

Data:

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Not applicable.

The Applicant's Position:

The duration of exposure to study treatment was determined by the number of months exposed to infigratinib. Demographics, baseline disease characteristics, and prior anticancer therapies were summarized. Prior anticancer therapies were summarized by ATC code (WHO Drug Dictionary B3 Global September 2019) . Unless noted otherwise, all adverse events (AEs) are treatment-emergent AEs, defined as an AE that started on or after the first dose date and up to 30 days after last dose date of infigratinib.

Search strategies for predefined adverse events of special interest (AESI) used Standardized MedDRA Queries (SMQs) and/or sponsor-defined grouped PTs using MedDRA 21.0, as outlined in the SAP. On treatment death was defined as a death that occurred after first dose of study drug (infigratinib) and within 30 days of the last dose of study drug (infigratinib). Integrated analyses of ECG results, clinical labs, and vital signs and physical findings were also conducted.

Adverse events of special interest (AESIs) evaluated include event categories based on class effect, mechanism of action, and the clinical experience to date with infigratinib: calcium phosphate homeostasis (including the subcategories of hypercalcemia, hyperphosphatemia, and hypophosphatemia); eye disorder, including a subset for CSR/RPED; cardiac disorder; acute pancreatitis; pathological fracture; tissue calcification; vascular calcification/mineralization.

The FDA's Assessment:

FDA agrees with the Applicant's description of the safety review approach.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Overall exposure to infigratinib is presented in Table 36 below.

Table 36: Exposure to Infigratinib (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Duration of treatment (months)		
Mean (SD)	4.80 (5.95)	6.39 (4.66)
Median	3.06	5.52
Min, max	0.03, 62.00	0.03, 28.29
≤2 months	153 (43.6)	18 (16.7)
>2 to ≤4 months	68 (19.4)	22 (20.4)
>4 to ≤6 months	37 (10.5)	17 (15.7)
>6 to ≤8 months	34 (9.7)	21 (19.4)
>8 to ≤10 months	15 (4.3)	10 (9.3)
>10 to ≤12 months	8 (2.3)	7 (6.5)
>12 months	36 (10.3)	13 (12.0)
Cumulative actual dose (mg)		
Mean (SD)	10579.3 (10450.89)	13691.9 (9284.88)
Median	7825.0	12225.0
Min, max	125, 69045	125, 51150
Relative dose intensity (%) ^a		
Mean (SD)	85.2 (20.05)	77.9 (17.58)
Median	88.1	78.0
Min, max	31, 133	38, 105
≤50%	15 (4.3)	4 (3.7)
>50 to ≤75%	94 (26.8)	44 (40.7)
>75 to ≤90%	73 (20.8)	24 (22.2)
>90 to ≤100%	119 (33.9)	30 (27.8)
>100%	50 (14.2)	6 (5.6)
max=maximum; min=minimum; SD=standard deviation.		
^a Relative dose intensity = actual cumulative dose (mg) / planned cumulative dose (mg) within the actual treatment duration.		
Source: 2.7.4 Summary of Clinical Safety, Table 1; adsl.xpt, adex.xpt		

The Applicant's Position:

Median exposure in the primary safety analysis set (5.52 months [min, max: 0.03, 28.29]) was longer compared to the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis [3.06 months (min, max: 0.03, 62.00)], which could account for some differences in AE incidences. These exposures are considered appropriate to allow for an adequate assessment

of safety in subjects who were representative of the intended target population.

The FDA's Assessment:

FDA confirms the median exposure in the 108-patient primary safety analysis set of 5.52 months (min, max: 0.03, 28.29). As summarized in Table 42, 89% of patients in Study 2204 discontinued treatment with infigratinib at the time of the primary analysis; 62% of patients discontinued treatment because of disease progression. Although the median exposure in Study 2204 is longer than the exposure in the pooled referenced population, it represents the population for which infigratinib will be marketed.

Relevant characteristics of the safety population:

Data:

A summary of the demographics and baselines characteristics of the safety population are provided in Table 37, Table 38, and Table 39 below.

Table 37: Subject Demographics (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Region, n (%) ^a		
North America	238 (67.8)	77 (71.3)
Europe	94 (26.8)	24 (22.2)
Asia	14 (4.0)	7 (6.5)
ROW	5 (1.4)	0
Race, n (%)		
White	284 (80.9)	78 (72.2)
Black or African American	14 (4.0)	4 (3.7)
Asian	27 (7.7)	11 (10.2)
Other/Unknown	26 (7.4)	15 (13.9)
Age, years		
Mean (SD)	58.3 (12.81)	53.4 (13.08)
Median	60.0	53.0
Min, max	20, 85	23, 81
Age group, n (%)		
18 to <65 years	236 (67.2)	82 (75.9)
≥65 years	115 (32.8)	26 (24.1)
≥75 years	35 (10.0)	NA

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Sex, n (%)		
Male	169 (48.1)	41 (38.0)
Female	182 (51.9)	67 (62.0)
BMI (kg/m ²)		
N	344	102
Mean (SD)	26.0 (5.71)	26.4 (6.64)
Median	25.1	25.5
Min, max	15.7, 50.6	16.0, 50.6
BMI=body mass index; max=maximum; min=minimum; NA=not applicable or not done for the dataset; ROW=rest of the world; SD=standard deviation. ^a For region, North America includes the US; Europe includes Austria, Germany, Spain, France, Italy, the Netherlands, Slovakia, Belgium, and Switzerland; Asia includes China, Japan, Singapore, Thailand, Korea, and Taiwan; ROW includes Australia, Israel, and Russia. Source: 2.7.4 Summary of Clinical Safety, Table 4; adsl.xpt		

Table 38: Baseline Disease Characteristics (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/ 1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
ECOG PS, n (%)		
0	120 (34.2)	45 (41.7)
1	210 (59.8)	62 (57.4)
2	21 (6.0)	1 (0.9)
Primary site of cancer, n (%) ^a		
Cholangiocarcinoma/bile duct/liver	135 (38.5)	108 (100.0)
Bladder	66 (18.8)	0
Glioblastoma	29 (8.3)	0
Lung	24 (6.8)	0
Head and neck	16 (4.6)	0
Breast	15 (4.3)	0
Colorectal	12 (3.4)	0
UTUC	10 (2.8)	0
Ovarian	8 (2.3)	0
Other or Unknown	36 (10.3)	0
Metastatic status, n (%)		
No metastatic site	38 (10.8)	5 (4.6)
Had metastatic site(s)	313 (89.2)	102 (94.4)
Lung	195 (55.6)	74 (68.5)
Liver	185 (52.7)	ND ^d
Node	161 (45.9)	62 (57.4)
Bone	93 (26.5)	28 (25.9)
Brain	4 (1.1)	0
Other	148 (42.2)	41 (38.0)
Time from initial diagnosis to first dose day, months		
N	340	108
Mean (SD)	34.00 (35.00)	21.73 (24.77)
Median	21.39	12.75
Min, max	1.74, 192.69	1.74, 152.94

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	125 mg 3 Weeks On/ 1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Time from the most recent recurrence/ progression to the first dose day, months		
N	331	98
Mean (SD)	2.75 (3.82)	2.20 (2.71)
Median	1.68	1.40
Min, max	0.03, 33.51	0.03, 14.59
Histological grade, n (%)		
Well differentiated	32 (9.1)	9 (8.3)
Moderately differentiated	96 (27.4)	42 (38.9)
Poorly differentiated	106 (30.2)	33 (30.6)
Undifferentiated	13 (3.7)	1 (0.9)
Unknown/missing	98 (27.9)	22 (20.4)
Not applicable	ND	1 (0.9)
Stage at time of study entry, n (%)		
Stage II	2 (0.6)	1 (0.9)
Stage III	5 (1.4)	0
Stage IV	145 (41.3)	107 (99.1)
Not reported ^b	199 (56.7)	0
Prior antineoplastic regimen		
No	10 (2.8)	0
Yes	341 (97.2)	108 (100.0)
1	97 (27.6)	42 (38.9)
2	99 (28.2)	35 (32.4)
3	62 (17.7)	16 (14.8)
≥4	83 (23.6)	15 (13.9)
FGFR2 fusions or other rearrangements		
Yes	117 (33.3)	108 (100.0)
No ^c	234 (66.7)	0
Baseline renal function (CrCl, mL/min)		
≥90	165 (47.0)	71 (65.7)
60 to <90	119 (33.9)	29 (26.9)
45 to <60	46 (13.1)	7 (6.5)
<45	21 (6.0)	1 (0.9)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	125 mg 3 Weeks On/ 1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
CrCl=creatinine clearance; ECOG PS=Eastern Cooperative Oncology Group performance status; max=maximum; min=minimum; ND=not done for the dataset; SD=standard deviation; UTUC=upper tract urothelial carcinoma.		
^a A primary cancer representing ≥2.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set is listed individually in this table. A primary cancer representing <2.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set is included in the “other” category for this table. ISS Table 14.1.3.1 lists all primary cancer types, including those representing <2% of all subjects. ^b Stage at study entry was not available for CBGJ398X2101 and CBGJ398XUS04. ^c “No” group includes subjects with either test results not available or results associated with other FGFR 1, 2, 3 alterations. ^d For the primary safety analysis set, only non-liver metastatic status is provided. Source: 2.7.4 Summary of Clinical Safety, Table 5; adsl.xpt		

Table 39: Prior Antineoplastic Medications Taken by ≥5.0% of All Subjects (125 mg 3 Weeks On/1 Week Off Schedule Monotherapy Safety Analysis Set; Primary Safety Analysis Set)

	125 mg 3 Weeks On/ 1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Any prior antineoplastic therapy, n (%)	341 (97.2)	108 (100.0)
Platinum compounds	275 (78.3)	104 (96.3)
Cisplatin	185 (52.7)	84 (77.8)
Carboplatin	100 (28.5)	14 (13.0)
Oxaliplatin	54 (15.4)	27 (25.0)
Pyrimidine analogues	257 (73.2)	107 (99.1)
Gemcitabine	187 (53.3)	90 (83.3)
Fluorouracil	65 (18.5)	26 (24.1)
Capecitabine	53 (15.1)	20 (18.5)
Gemcitabine hydrochloride	49 (14.0)	25 (23.1)
Taxanes	106 (30.2)	15 (13.9)
Paclitaxel	73 (20.8)	7 (6.5)
Docetaxel	40 (11.4)	2 (1.9)
Monoclonal antibodies	89 (25.4)	8 (7.4)
Bevacizumab	52 (14.8)	6 (5.6)
Other antineoplastic agents	53 (15.1)	13 (12.0)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

	125 mg 3 Weeks On/ 1 Week Off Schedule Monotherapy Safety Analysis Set	Primary Safety Analysis Set
	All Subjects (N = 351)	All Subjects (N = 108)
Irinotecan	27 (7.7)	11 (10.2)
Detoxifying agents for antineoplastic treatment	43 (12.3)	17 (15.7)
Folinic acid	31 (8.8)	11 (10.2)
Anthracyclines and related substances	42 (12.0)	0
Doxorubicin	30 (8.5)	0
Protein kinase inhibitors	41 (11.7)	15 (13.9)
Vinca alkaloids and analogues	31 (8.8)	1 (0.9)
Other alkylating agents	28 (8.0)	0
Temozolomide	26 (7.4)	0
Combinations of antineoplastic agents	28 (8.0)	12 (11.1)
Other immunostimulants	24 (6.8)	0
BCG vaccine	19 (5.4)	0
Nitrogen mustard analogues	18 (5.1)	0
Other immunosuppressants	18 (5.1)	0
Methotrexate	18 (5.1)	0
BCG=bacille Calmette-Guerin. Multiple occurrences of the same medication within each subject are only counted once at each level of summation by overall, ATC, preferred term. Medications are coded using WHO Drug Dictionary. All ATC classes are included. Individual medications within each ATC class taken by ≥5.0% of all subjects in the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set are listed individually in this table. Source: 2.7.4 Summary of Clinical Safety, Table 6; adsl.xpt		

The Applicant's Position:

The eligibility criteria in Study CBGJ398X2204 were clinically relevant for the target population of subjects who would receive infigratinib following regulatory approval in the proposed indication. The study enrolled patients with advanced or metastatic cholangiocarcinoma with FGFR genetic alterations who had progressed after receiving at least one prior antineoplastic treatment regimen containing gemcitabine with or without cisplatin. Demographic characteristics were representative of the refractory patient population, thereby providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study population in Table 38 and Table 39 for the primary safety analysis set above. These characteristics reflect the patient population intended for use of infigratinib. Compared to the monotherapy safety analysis set of 351

patients, the patients in Study CBGJ398X2204 have a younger median age and a higher percentage are female, which are consistent with the demographics observed in patients with FGFR-rearranged cholangiocarcinoma.

Of note, “prior antineoplastic regimen” refers to systemic chemotherapy. Consistent with the eligibility requirements of Study CBGJ398X2204, all 108 patients received prior systemic chemotherapy (though this could have been in the perioperative setting and, therefore, classified as neoadjuvant or adjuvant chemotherapy).

Additionally, although there were three different formulations of infigratinib (FMI I, FMI III, and FMI IV) used in Study 2204, any safety differences among these formulations could not be assessed due to the low number of patients who received FMI IV (n = 9).

Adequacy of the safety database:

Data:

The clinical development program contributing to the safety analysis for this marketing application comprises 17 clinical studies, with 797 subjects exposed to infigratinib. The overall safety review is focused on data from the primary safety analysis set (108 subjects; median exposure of 5.52 months) and the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set (351 subjects; median exposure of 3.06 months). In both analysis sets, subjects received infigratinib monotherapy on the 125 mg 3 weeks on/1 week off schedule. The exposures in both analysis sets are also considered appropriate to allow for an adequate assessment of safety in subjects who were representative of the intended target population.

The Applicant’s Position:

The safety database is adequate for an informed assessment of the safety profile of infigratinib and an informed evaluation of the overall risk-benefit in subjects with advanced or metastatic cholangiocarcinoma.

The FDA’s Assessment:

FDA concurs with the Applicant’s assessment of the adequacy of the safety database.

8.2.3. Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not applicable.

The Applicant's Position:

No concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these are sufficiently complete to allow for a thorough review of safety.

The FDA's Assessment:

FDA acknowledges the Applicant's position; the review did not uncover any data integrity issues. FDA agrees the BLA submission was complete.

Categorization of Adverse Event

The Applicant's Position:

AEs were graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) 3.0 and above, determined by the version of CTCAE defined in each protocol. Grades ranging from 1 to 4 generally correspond to mild, moderate, severe, and life-threatening. Because Grade 5 AE severity was not a choice in the design of the databases of all the monotherapy studies, AEs with fatal outcome were presented via on treatment death summaries, where death reason was coded, and on treatment death was summarized by system organ class (SOC) and PT.

For integrated analyses, AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. In the monotherapy analysis set, data collection and case report forms were different across studies. In the databases of studies CBGJ398X2101 and CBGJ398XUS04, AE outcome data collection was limited to a check box on the case report form to indicate whether an AE was ongoing. This information was used to determine whether an AE resolved. AEs with fatal outcome were collected and coded as described above.

Search strategies for predefined adverse events of special interest (AESI) used Standardised MedDRA Queries (SMQs) and/or sponsor-defined grouped PTs using MedDRA 21.0. The predefined AESI categories were calcium-phosphate homeostasis (hypercalcemia, hyperphosphatemia, and hypophosphatemia), eye disorder, central serous chorioretinopathy/retinal pigment epithelial detachment (CSR/RPED), cardiac disorder, acute pancreatitis, pathological fracture, tissue calcification, and vascular/intravascular mineralization. Search terms for sponsor-defined grouped PTs are listed in Section 13.1 of the ISS SAP. Medical history search strategies (listed in Section 13.8 of the ISS SAP) were used to identify potentially important medical history as risk factors for the occurrence of selected AESIs in addition to past occurrences of those selected AESIs.

The FDA's Assessment:

FDA agrees with the Applicant's summary. For Study CBGJ398X2204, AEs were assessed by the investigator according to CTCAE v4.03 criteria and were coded using MedDRA version 21.0. Adverse events were assessed during the treatment period and for 30 days after the last dose

of study drug.

FDA conducted an audit of the safety datasets. Verbatim terms for safety events were accurately coded using the MedDRA dictionary; differences between the verbatim terms and the preferred terms are mostly related to differences in spelling or the use of common medical terms. FDA also agrees with the grading of events in most cases but not all (i.e., a sepsis was coded as Grade 3, which is incorrect, etc.).

Routine Clinical Tests

Data:

Not Applicable.

The Applicant's Position:

Laboratory values were graded programmatically using CTCAE version 4.03, or as otherwise specified in the SAP. Laboratory parameters for hematology and serum blood chemistry were summarized at baseline and each postbaseline visit. The maximum and minimum observed postbaseline values, last observed values, and changes from baseline were summarized. Shift tables for shifts in laboratory parameters from baseline to worst CTCAE grade observed postbaseline were prepared. In addition, the number and percentage of subjects with postbaseline laboratory abnormal results was presented for tests based on CTCAE grade, or normal range if CTCAE grade was not available. Incidence of potential drug-induced liver injury, based on AST, ALT, TBL, and ALP, was presented. Potential Hy's law cases were also listed. Ophthalmic assessments, ECG, and LVEF, vital signs, and ECOG PS were summarized using descriptive statistics or categorical presentations, as appropriate.

The FDA's Assessment:

FDA agrees with the Applicant's description. Patients were tested for routine monitoring on Days 1, 8, and 15 of Cycle 1, Days 1 and 15 of Cycle 2, and on Day 1 of each cycle thereafter. As CTCAE v4.03 does not specifically describe hyperphosphatemia, the Applicant classified serum phosphate levels as follows:

- <2.5 mg/dL (<0.8075 mmol/L)
- ≥2.5 to ≤5.5 mg/dL (≥0.8075 to ≤1.7765 mmol/L) (normal range for this assessment to align with dose modification schema in study protocols)
- >5.5 to ≤7.5 mg/dL (>1.7765 to ≤2.4225 mmol/L)
- >7.5 to <9.0 mg/dL (>2.4225 to <2.907 mmol/L)
- ≥9.0 mg/dL (≥2.907 mmol/L)

8.2.4. Safety Results

The 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set (351 subjects from studies CBGJ398X2101, CBGJ398X2201, CBGJ398X2204, and CBGJ398XUS04) and the primary safety analysis set (108 subjects from study CBGJ398X2204) both received infigratinib monotherapy on the 125 mg 3 weeks on/1 week off schedule (ie, dosing in the proposed infigratinib label), and both had comparable median exposures. As such, given that review of safety data from these analysis sets identified no overall clinically meaningful differences, this section will focus on safety data from the primary safety analysis.

Deaths

Data:

Table 40 below summarizes the primary reasons for deaths that occurred during the study. The on-treatment period was defined as the period of time from the day of first dose to the day of last dose +30 days (inclusive). The posttreatment period was defined as any time after the day of last dose +30 days.

Table 40: Primary Reasons for Death (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Category	All Subjects (N=108) n (%)
Overall Death	70 (64.8)
Study Indication	62 (57.4)
Other	8 (7.4)
Death during the on-treatment period ^a	5 (4.6)
Study Indication	5 (4.6)
Death during the posttreatment period	65 (60.2)
Study Indication	57 (52.8)
Other	8 (7.4)
^a A sixth subject had an on-treatment TEAE with a fatal outcome (Grade 4 sepsis). The subject died 36 days after her last study treatment, so the death was not summarized here as on-treatment, but the TEAE of sepsis that led to death started 7 days after the last study treatment. In this table, this subject is included in the category "Other" under "Death during the posttreatment period." Source: CBGJ398X2204 CSR, Table 36; adsl.xpt, adef.xpt, adtte.xpt	

The Applicant's Position:

For Study CBGJ398X2204, seventy subjects (64.8%) died during the study: 62 subjects (57.4%) died due to the study indication and 8 subjects (7.4%) died due to other causes (Table 40). Of the 70 deaths that occurred during the study, 65 occurred during the posttreatment period, and 5 occurred during the on-treatment period.

The 5 deaths that occurred during the on-treatment period were due to the study indication (cholangiocarcinoma). A sixth subject had an on-treatment TEAE with a fatal outcome (Grade 4 sepsis, not related to study treatment). The subject had a TEAE of sepsis which started 7 days after the last study treatment and died of sepsis 36 days after the last study dose, so the subject's death was not captured as on-treatment. A review of AEs by subgroup for fatal outcomes did not identify any patterns.

The FDA's Assessment:

FDA agrees with the Applicant's analysis; most deaths were related to disease progression and expected complications of advanced cancer of the biliary tract/liver. A review of the data and narratives of the eight patients whose deaths were not attributed to disease progression (listed as due to "other" or "unknown" causes) was conducted. Four patients had further documentation of disease progression with the date of discontinuation of study drug preceding the date of death by 95-267 days. Causes of death for the remaining patients include upper GI hemorrhage (113 days after discontinuation of study drug), hepatic failure (patient discontinued treatment due to progression of disease and subsequently died from hepatic failure 101 days later), sepsis (35 days after discontinuation of study drug), and "other/unknown" (approximately two and a half years after the last dose of infigratinib after discontinuing infigratinib due to progression of disease).

Serious Adverse Events

Data:

SAEs occurred in 31.5% of subjects in the primary data analysis set, and are summarized in Table 41 below. SAEs were reported, regardless of suspected causality, from date of signed ICF and until 30 days after the last dose of study drug. Progression of underlying malignancy was not reported as an AE or SAE if it was clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol.

Table 41: Serious Treatment Emergent Adverse Events That Occurred in >1 Subject by System Organ Class and Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

System Organ Class/ Preferred Term	All Subjects (N=108) n (%)
Any Treatment Emergent SAE	34 (31.5)
Metabolism and nutrition disorders	6 (5.6)
Hypercalcaemia	3 (2.8)
Hypophosphataemia	2 (1.9)
Gastrointestinal disorders	11 (10.2)
Abdominal pain	2 (1.9)
Abdominal pain upper	2 (1.9)
Ascites	2 (1.9)
Constipation	2 (1.9)
General disorders and administration site conditions	8 (7.4)
Pyrexia	4 (3.7)
Infections and infestations	11 (10.2)
Sepsis	3 (2.8)
Cellulitis	2 (1.9)
Infection	2 (1.9)
Respiratory, thoracic and mediastinal disorders	2 (1.9)
Pleural effusion	2 (1.9)
Blood and lymphatic system disorders	4 (3.7)
Anaemia	4 (3.7)
Renal and urinary disorders	3 (2.8)
Acute kidney injury	2 (1.9)
Hepatobiliary disorders	3 (2.8)
Cholangitis	2 (1.9)
Abbreviations: SAE=serious adverse event. Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order. Source: CBGJ398X2204 CSR, Table 37, Table 14.3.1.2.35 adsl.xpt, adae.xpt	

The Applicant's Position:

Overall, these SAEs could be attributed to on-target effects of infigratinib (eg, hypercalcemia), underlying disease (eg, abdominal pain, anemia of chronic disease), or an infection (eg, pyrexia, sepsis, etc.). The most common SAEs were anemia (3.7%), pyrexia (3.7%), hypercalcemia (2.8%), and sepsis (2.8%). Overall, 1 subject (0.9%) had a Grade 1 SAE, 5 subjects (4.6%) had at least 1 SAE with a maximum severity of Grade 2, 24 subjects (22.2%) had at least 1 Grade 3 SAE, and 4 subjects (3.7%) had at least 1 Grade 4 SAE. Grade 3 SAEs that occurred in >1 subject were anemia, abdominal pain, ascites, cellulitis, infection, hypercalcemia, hypophosphatemia, acute kidney injury, and pleural effusion (2 subjects [1.9%] each). Grade 4 SAEs consisted of sepsis, stress fracture, and hypercalcemia.

The FDA's Assessment:

FDA replicated QED's of SAEs summarized in Table 41, but combined the two preferred terms (PT) for abdominal pain to calculate a 3.7% incidence. Grade 3 SAEs that occurred in more than one patient were: abdominal pain, acute kidney injury (AKI), anemia, ascites, cellulitis, hypercalcemia, hypophosphatemia, infection, pleural effusion. Four patients experienced a total of five Grade 4 SAEs with the following PTs: sepsis, stress fracture, and hypercalcemia.

FDA agrees that the nature of the reported SAEs are consistent with the disease under study and with the expected toxicities of infigratinib.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 42 below describes subject disposition in Study CBGJ398X2204 (Interim Analysis Set 2 for Cohort 1). Subjects discontinued study treatment most often due to progressive disease (62.0%), AEs (13.9%), or physician decision (8.3%).

Table 42: Subject Disposition (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

	All Subjects (N=108) n (%)
Subjects received study treatment	108 (100.0)
Subjects with treatment ongoing	12 (11.1)
Subjects ended treatment	96 (88.9)
AE	15 (13.9)
Death	1 (0.9)
Progressive disease	67 (62.0)
Physician decision	9 (8.3)
Subject decision or withdrawal of consent	3 (2.8)
Missing	1 (0.9)
Abbreviations: AE=adverse event. Note: A subject was considered to have ended treatment if "dose permanently discontinued" was flagged on the dosing form and/or on the End of Treatment form; the date of discontinuation and/or reason was filled out. Source: CBGJ398X2204 CSR, Table 8; adsl.xpt	

Table 43 below presents subject incidence of AEs that led to treatment discontinuation in Study CBGJ398X2204 (Interim Analysis Set 2 Cohort 1).

Table 43: Treatment Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class/Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

System Organ Class/ Preferred Term	All Subjects (N=108) n (%)
Any TEAE Leading to Discontinuation	16 (14.8)
Grade 1	4 (3.7)
Grade 2	7 (6.5)
Grade 3	3 (2.8)
Grade 4	2 (1.9)
Cardiac disorders	1 (0.9)
Atrial fibrillation	1 (0.9)
Grade 2	1 (0.9)
Eye disorders	3 (2.8)
Subretinal fluid	2 (1.9)
Grade 2	2 (1.9)
Chorioretinal scar	1 (0.9)
Grade 1	1 (0.9)
Vision blurred	1 (0.9)
Grade 2	1 (0.9)
Gastrointestinal disorders	1 (0.9)
Ascites	1 (0.9)
Grade 3	1 (0.9)
General disorders and administration site conditions	3 (2.8)
Fatigue	2 (1.9)
Grade 1	1 (0.9)
Grade 3	1 (0.9)
Calcinosis	1 (0.9)
Grade 1	1 (0.9)
Infections and infestations	1 (0.9)
Sepsis	1 (0.9)
Grade 3	1 (0.9)
Injury, poisoning and procedural complications	1 (0.9)
Stress fracture	1 (0.9)
Grade 4	1 (0.9)
Investigations	3 (2.8)
Blood creatinine increased	2 (1.9)
Grade 2	2 (1.9)
Lipase increased	1 (0.9)
Grade 4	1 (0.9)
Metabolism and nutrition disorders	1 (0.9)
Calciophylaxis	1 (0.9)
Grade 1	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (0.9)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

System Organ Class/ Preferred Term	All Subjects (N=108) n (%)
Bone pain	1 (0.9)
Grade 2	1 (0.9)
Renal and urinary disorders	1 (0.9)
Acute kidney injury	1 (0.9)
Grade 3	1 (0.9)
Skin and subcutaneous tissue disorders	1 (0.9)
Nail disorder	1 (0.9)
Grade 2	1 (0.9)
Skin exfoliation	1 (0.9)
Grade 2	1 (0.9)

Abbreviations: TEAE=treatment-emergent adverse event.
Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order.
Source: CBGJ398X2204 CSR, Table 39; adsl.xpt, adae.xpt

The Applicant's Position:

For Study CBGJ398X2204, most subjects (62.0%) who discontinued infigratinib treatment did so due to disease progression rather than an AE (Table 42). Sixteen subjects (14.8%) had a total of 20 TEAEs that led to treatment discontinuation (Table 43). Generally, AEs that led to discontinuation of study drug could be attributed to on-target effects of infigratinib, underlying disease, and/or its consequences. Eleven of these subjects had an event that was Grade 1 (3.7%) or Grade 2 (6.5%) in intensity; the remaining 5 subjects had a Grade 3 (2.8%) or Grade 4 (1.9%) event. TEAEs that led to treatment discontinuation in >1 subject were subretinal fluid, fatigue, and increased blood creatinine (2 subjects [1.9%] each). Three of the 16 subjects (18.8%) who discontinued treatment discontinued due to an ocular TEAE.

The FDA's Assessment:

FDA agrees with the Applicant's analysis summarized in the "Subject Disposition" table above (except the sepsis Grade 3, see above). Sixteen patients (15%) discontinued study drug due to AEs. For the purposes of analysis and signal seeking, FDA combined the preferred terms "blood creatinine increased" with "acute kidney injury" to total three such events (2.8%) and combined "calcinosis" with "calciophylaxis" to total two such events (1.9%). Of note, eye disorders were the most common cause of treatment discontinuation (4 patients, 3.7%);

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 44 and Table 45 below present subject incidence of AEs that led to dose interruption/dose reduction in Study CBGJ398X2204 (Interim Analysis Set 2 Cohort 1).

Table 44: Treatment Emergent Adverse Events Leading to Dose Interruption in >2 Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Preferred Term	All Subjects (N=108) n (%)
Any TEAE Leading to Dose Interruption	69 (63.9)
Grade 1	4 (3.7)
Grade 2	27 (25.0)
Grade 3	36 (33.3)
Grade 4	2 (1.9)
Hyperphosphataemia	26 (24.1)
Hypercalcaemia	9 (8.3)
Palmar-plantar erythrodysaesthesia syndrome	8 (7.4)
Stomatitis	7 (6.5)
Diarrhoea	6 (5.6)
Blood creatinine increased	5 (4.6)
Vomiting	5 (4.6)
Anaemia	4 (3.7)
Hypophosphataemia	4 (3.7)
Chorioretinopathy	3 (2.8)
Fatigue	3 (2.8)
Hyponatraemia	3 (2.8)
Lipase increased	3 (2.8)
Pyrexia	3 (2.8)
Vision blurred	3 (2.8)
Abbreviations: TEAE=treatment-emergent adverse event. Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order. Source: CBGJ398X2204 CSR, Table 40; adsl.xpt, adae.xpt	

Table 45: Treatment Emergent Adverse Events Leading to Dose Adjustment in >2 Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Preferred Term	All Subjects (N=108) n (%)
Any TEAE Leading to Dose Adjustment	65 (60.2)
Grade 1	10 (9.3)
Grade 2	26 (24.1)
Grade 3	29 (26.9)
Hyperphosphataemia	28 (25.9)
Stomatitis	13 (12.0)
Palmar-plantar erythrodysaesthesia syndrome	9 (8.3)
Blood creatinine increased	4 (3.7)
Lipase increased	4 (3.7)
Hypercalcaemia	3 (2.8)
Onycholysis	3 (2.8)
Abbreviations: TEAE=treatment-emergent adverse event.	

Preferred Term	All Subjects (N=108) n (%)
Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order. Source: CBGJ398X2204 CSR, Table 41; adsl.xpt, adae.xpt	

The Applicant's Position:

Dose Interruption: Sixty-nine subjects (63.9%) had at least 1 TEAE that led to dose interruption for Study CBGJ398X2204 ([Table 44](#)); 36 (33.3%) had at least 1 Grade 3 event and 2 (1.9%) had a Grade 4 event. The one TEAE that led to dose interruption in $\geq 10\%$ of all subjects was hyperphosphatemia (26 subjects [24.1%]), an on-target effect of infigratinib.

Grade 4 TEAEs that led to dose interruption were sepsis and cataract (1 subject [0.9%] each).

Dose adjustment: Sixty-five subjects (60.2%) had at least 1 TEAE that led to dose adjustment for Study CBGJ398X2204 ([Table 45](#)); 29 (26.9%) had at least 1 Grade 3 event and none had a Grade 4 event. TEAEs that led to dose adjustment in $\geq 10\%$ of all subjects were hyperphosphatemia (28 subjects [25.9%]) and stomatitis (13 subjects [12.0%]), both of which are on-target effects of infigratinib.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The majority of patients (64%) required dose interruptions for the management of toxicity. FDA replicated the analysis in Table 45 but grouped the preferred terms "hyperphosphatemia" and "blood phosphorus increased" to yield an incidence of 25% and "blood creatinine increased" and "acute kidney injury" should be combined to yield 6%

FDA agrees with the Applicant's assessment that 65 patients (60%) required dose-adjustment (reduction) due to AEs; 28% patients required dose reductions for hyperphosphatemia (grouping the PTs "hyperphosphatemia" and "blood phosphorus increased").

The events leading to dose interruptions and reductions are consistent with the AE profile of infigratinib in this disease setting but the high rate of dose modifications questions the overall tolerability of the proposed dosage.

Significant Adverse Events

Data:

Significant adverse events are described in [Section 8.2.5](#) of this document.

The Applicant's Position:

Significant adverse events are described in [Section 8.2.5](#) of this document.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 46 and Table 47 below present subject incidence of TEAEs ($\geq 10\%$) and adverse reactions ($\geq 15\%$) in Study CBGJ398X2204 (Interim Analysis Set 2 Cohort 1).

Table 46: Treatment Emergent Adverse Events Occurring in $\geq 10\%$ of All Subjects by Preferred Term (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Preferred Term	All Subjects (N=108) n (%)
Hyperphosphataemia	83 (76.9)
Stomatitis	59 (54.6)
Fatigue	43 (39.8)
Alopecia	41 (38.0)
Dry eye	37 (34.3)
Palmar-plantar erythrodysaesthesia syndrome	36 (33.3)
Arthralgia	34 (31.5)
Dysgeusia	34 (31.5)
Constipation	32 (29.6)
Dry mouth	27 (25.0)
Hypercalcaemia	27 (25.0)
Blood creatinine increased	26 (24.1)
Diarrhoea	26 (24.1)
Dry skin	25 (23.1)
Decreased appetite	24 (22.2)
Hypophosphataemia	24 (22.2)
Aspartate aminotransferase increased	23 (21.3)
Vision blurred	23 (21.3)
Vomiting	23 (21.3)
Anaemia	20 (18.5)
Nausea	20 (18.5)
Epistaxis	19 (17.6)
Nail discolouration	19 (17.6)
Abdominal pain	18 (16.7)
Dyspepsia	18 (16.7)
Headache	18 (16.7)
Pain in extremity	18 (16.7)
Onychomadesis	17 (15.7)
Alanine aminotransferase increased	16 (14.8)
Blood alkaline phosphatase increased	16 (14.8)
Nail disorder	16 (14.8)
Pyrexia	16 (14.8)
Weight decreased	16 (14.8)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Preferred Term	All Subjects (N=108) n (%)
Back pain	15 (13.9)
Abdominal pain upper	14 (13.0)
Hyponatraemia	14 (13.0)
Insomnia	14 (13.0)
Myalgia	14 (13.0)
Oedema peripheral	14 (13.0)
Onychalgia	14 (13.0)
Cough	13 (12.0)
Lacrimation increased	13 (12.0)
Onycholysis	13 (12.0)
Blepharitis	12 (11.1)
Lipase increased	12 (11.1)
Trichiasis	12 (11.1)
Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order. Source: CBJ398X2204 CSR, Table 31; adsl.xpt, adae.xpt	

Table 47: Adverse Reactions (≥15%) in Patients Receiving Infigratinib in Study CBJ398X2204

Adverse Reaction	N=108	
	All Grades (%)	Grades ≥3 ^a (%)
Metabolism and nutrition disorders		
Hyperphosphatemia ^b	78	11
Hypercalcemia	25	6
Hypophosphatemia	22	13
Decreased appetite	22	1
Skin and subcutaneous tissue disorders		
Nail toxicity ^c	57	2
Alopecia	38	0
Palmar-plantar erythrodysesthesia syndrome	33	7
Dry skin	23	0
Gastrointestinal disorders		
Stomatitis ^d	56	15
Constipation	30	1
Dry mouth	25	0
Diarrhea	24	3
Vomiting	21	1
Nausea	19	1
Abdominal pain	17	4
Dyspepsia	17	0
Eye disorders		
Dry eye ^e	44	2
Eyelash changes ^f	25	0

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Adverse Reaction	N=108	
	All Grades (%)	Grades ≥3 ^a (%)
Vision blurred	21	0
General disorders and administrative site conditions		
Fatigue ^g	44	4
Musculoskeletal and connective tissue disorders		
Arthralgia	32	0
Pain in extremity	17	2
Nervous system disorders		
Dysgeusia	32	0
Headache	17	1
Investigations		
Blood creatinine increased	24	0
Aspartate aminotransferase increased	21	2
Blood and lymphatic system disorders		
Anemia	19	4
Respiratory, thoracic and mediastinal disorders		
Epistaxis	18	0
Graded according to NCI CTCAE 4.03.		
^a Only Grades 3 and 4.		
^b Includes hyperphosphatemia and blood phosphorous increased.		
^c Includes ingrown nail, nail bed bleeding, nail bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail hypertrophy, nail infection, nail ridging, onychalgia, onychoclasia, onycholysis, onychomadesis, onychomycosis, and paronychia.		
^d Includes mouth ulceration and stomatitis.		
^e Includes dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis.		
^f Includes blepharitis, eyelash changes, eyelash discoloration, growth of eyelashes, trichiasis, and trichomegaly.		
^g Includes asthenia and fatigue.		
Source: USPI, Section 6.1, Table 3; adsl.xpt, adae.xpt		

The Applicant's Position:

Most Frequent AEs by Preferred Term: TEAEs that occurred in ≥10% of all subjects are presented in [Table 46](#). TEAEs reported in ≥30% of subjects were hyperphosphatemia (76.9%), stomatitis (54.6%), fatigue (39.8%), alopecia (38.0%), dry eye (34.3%), palmar-plantar erythrodysesthesia syndrome (33.3%), arthralgia (31.5%), and dysgeusia (31.5%).

Severity of AEs: Overall, 8 subjects (7.4%) had at least 1 TEAE with a maximum severity of Grade 1, 29 subjects (26.9%) had at least 1 Grade 2 TEAE, 61 subjects (56.5%) had at least 1 Grade 3 TEAE, and 9 subjects (8.3%) had at least 1 Grade 4 TEAE. Seventy subjects (64.8%) had at least 1 TEAE with a maximum severity of Grade 3 or Grade 4 (combined). Grade 3 or Grade 4 TEAEs that occurred in ≥5% of all subjects included stomatitis (14.8%), hyponatremia (13.0%), hypophosphatemia (13.0%), hyperphosphatemia (10.2%), increased lipase (6.5%), palmar-plantar erythrodysesthesia syndrome (6.5%), and hypercalcemia (5.6%).

Adverse Drug Reactions: The primary safety analysis set from Study CBGJ398X2204 was used to

determine the frequency of ADRs for the proposed infigratinib label (Table 47). AEs which would not have met the ADR screening selection strategy criteria (eg, ADR candidates with a very low occurrence rate, or single cases) were also taken into consideration and added as an ADR if deemed medically relevant and deemed related to infigratinib.

Overall, the ADRs observed with infigratinib were consistent with its mechanism of action and the toxicity observed in nonclinical studies. Most ADRs associated with infigratinib are predominantly Grade 1 or Grade 2 in severity, are consistent with the on-target effects of FGFR inhibition, and are easily monitored and managed in the clinical setting with concomitant medications, non-drug therapies, and dose modifications.

The FDA's Assessment:

FDA agrees with the types and frequencies of treatment-emergent AEs (TEAEs) listed in the table above. Of these, the AEs with frequencies of Grade 3-4 events $\geq 5\%$ were: stomatitis (15%), palmar-plantar erythrodysesthesia syndrome (PPES) (7%), and abdominal pain (composite term, 26% overall incidence and 5% Grade 3 incidence).

Clinically-relevant AEs that occurred at an incidence lower than 15% were cataract (12%) and fractures (1%).

Overall, FDA agrees that the observed safety profile is consistent with infigratinib's mechanism of action and the patient population studied. Although the majority of TEAEs were Grade 1-2, 64% of patients needed treatment interruption and 60% of patients needed dose adjustments for toxicity management.

Additionally, review of the 90-day safety update submission did not reveal any new safety findings with respect to the types of TEAEs being observed, TEAEs leading to dose modification or withdrawal, or the reasons for discontinuing treatment.

A revised table of TEAEs will be included in labeling.

AEs that reflect abnormal laboratory values (hyperphosphatemia, hypercalcemia, hypophosphatemia, blood creatinine increased, AST increased, and anemia) are analyzed below.

Laboratory Findings

Data:

Relevant laboratory findings for Study CBGJ398X2204 (primary safety analysis set) are summarized in Table 48 below.

Table 48: Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Receiving Infigratinib in Study CBGJ398X2204 (Interim Analysis Set 2 for Cohort 1)

Laboratory Abnormality	N=108	
	All Grades (%)	Grades ≥3 (%)
Hematology		
Decreased hemoglobin	51	5
Decreased lymphocytes	42	9
Decreased platelets	35	4
Decreased leukocytes	30	3
Decreased neutrophils	14	2
Chemistry		
Increased creatinine	95	7
Increased phosphate ^a	89	13
Decreased phosphate	63	31
Increased alkaline phosphatase	52	8
Increased alanine aminotransferase	51	6
Increased calcium	50	11
Increased lipase	45	8
Decreased sodium	41	20
Increased triglycerides	38	2
Increased aspartate aminotransferase	37	4
Increased urate	36	36
Decreased albumin	24	1
Increased bilirubin	24	6
Decreased potassium	22	3
Increased potassium	17	3
Increased cholesterol	16	1
The denominator used to calculate the rate varied from 94 to 107 based on the number of patients with a baseline value and at least one post-treatment value. Graded per NCI CTCAE 4.03. ^a NCI CTCAE 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades ≥3 defined as ≥9.0 mg/dL [≥2.907 mmol/L]). Source: ISS Tables 14.3.5.7.8.1.2, 14.3.5.7.9.1.1 (increased phosphate); adlb.xpt		

The Applicant's Position:

Hematologic abnormalities were mostly Grade 1 or Grade 2 in severity. Decreased hemoglobin was most commonly reported, which is not unexpected in the study population.

The clinical chemistry abnormalities were predominantly Grade 1 or Grade 2. Increased serum creatinine and increased/decreased phosphate were most commonly reported.

Of note, less than 10% of infigratinib is excreted renally. Despite the high percentage of subjects with Grade 1 and Grade 2 increased creatinine, few subjects had high grade (Grade 3

or 4) serum creatinine levels or reported acute renal failure/injury. Given the totality of the data, it is unlikely that infigratinib contributes to the development of acute kidney injury.

Increased serum phosphate is an on-target effect of infigratinib and is manageable with dose modifications and phosphate binders. Decreased serum phosphate could be due to over-correction; of note, approximately 80% of subjects took a concomitant phosphate binder.

The FDA's Assessment:

FDA confirms the lab abnormalities, calculated based on the highest grade of any adverse event using 108 as the denominator, as presented in the CSR. FDA's shift analysis is presented below in Table 49.

Table 49 - All Grade laboratory abnormalities occurring in $\geq 10\%$ of patients

	Overall N = 108	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Creatinine	100/107 (93)	7/107 (7)
Phosphate decreased	68/107 (64)	33/107 (31)
Alkaline phosphatase increased	58/107 (54)	9/107 (8)
Hemoglobin decreased	57/107 (53)	5/107 (4.7)
ALT increased	55/107 (51)	6/107 (6)
Corrected Calcium increased	53/107 (50)	12/107 (11)
Lipase increased	47/107 (44)	8/107 (7)
Calcium increased	46/107 (43)	8/107 (7)
Lymphocytes decreased	46/107 (43)	10/107 (9)
Sodium decreased	44/107 (41)	21/107 (20)
AST increased	41/107 (38)	4/107 (3.7)
Triglycerides increased	41/107 (38)	3/107 (2.8)
Urate increased	40/107 (37)	40/107 (37)
Platelets decreased	39/106 (37)	4/106 (3.8)
Magnesium decreased	35/104 (34)	0/0 (0.0)
Leukocytes decreased	28/107 (26)	3/107 (2.8)
Albumin decreased	26/107 (24)	1/107 (0.9)

	Overall N = 108	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Bilirubin increased	26/107 (24)	6/107 (6)
Potassium decreased	23/107 (21)	3/107 (2.8)
Cholesterol increased	19/107 (18)	1/107 (0.9)
Amylase increased	18/107 (17)	3/107 (2.8)
Potassium increased	18/107 (17)	3/107 (2.8)
Neutrophils decreased	15/107 (14)	2/107 (1.9)
Calcium decreased	11/107 (10)	2/107 (1.9)
PTT increased	1/6 (17)	0/0 (0.0)

FDA's calculations generally agree with the Applicant's. Lab abnormalities with incidence > 30% included increased creatinine, decreased phosphate, increased alkaline phosphatase, decreased hemoglobin, increased ALT, increased lipase, increased calcium, decreased lymphocytes, decreased sodium, increased AST, increased triglycerides, increased urate, decreased platelets, and increased magnesium. Hyperphosphatemia is discussed further in Section 8.2.5.2, below.

Overall, the liver lab abnormalities, the mineral metabolism lab abnormalities, and the hematologic lab abnormalities observed in Study 2204 are consistent with advanced cholangiocarcinoma in the setting of treatment and with the mechanism of action of infigratinib. The elevated creatinine may be a function of advanced disease state and dehydration but definitive conclusions cannot be made in this single-arm study.

Vital Signs

Data:

Overall, 14 subjects (13.0%) had a transient pulse of ≥ 100 bpm and increase from baseline $> 25\%$, and 2 subjects (1.9%) had a transient pulse of ≤ 50 bpm and decrease from baseline $> 25\%$. Two subjects (1.9%) had a systolic blood pressure ≥ 180 mmHg and increase from baseline ≥ 20 mmHg, and 9 subjects (8.3%) had a systolic blood pressure ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg. One subject (0.9%) had a diastolic blood pressure ≥ 105 mmHg and increase from baseline ≥ 15 mmHg, and 4 subjects (3.7%) had a diastolic blood pressure ≤ 50 mmHg and decrease from baseline ≥ 15 mmHg. No subjects had a temperature $\geq 39.1^\circ\text{C}$.

The Applicant's Position:

Other than pyrexia (14.8%), relatively few subjects ($\leq 4\%$) had a TEAE related to vital signs. All but one case of pyrexia was Grade 1 or Grade 2 in intensity; 1 (0.9%) subject had Grade 3

pyrexia.

The FDA's Assessment:

FDA review of vital signs data in the CSR did not raise any specific safety concerns.

Electrocardiograms (ECGs) and QT

Data:

ECGs and QTs for Study CBGJ398X2204 are summarized in Table 50 below.

Table 50: QT, QTcF, and QTcB Outlier Values (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1: Subjects with Both Baseline and Postbaseline ECG Assessment)

Sub-category	All Subjects (N=101) n (%)
Any outlier	54 (53.5)
QT outlier: new QT values >500 msec	0
QTcF outlier	
Any	30 (29.7)
New QTcF value >500 msec	0
New QTcF value >480 msec	1 (1.0)
New QTcF value >450 msec	14 (13.9)
QTcF change >30 to ≤60 msec	19 (18.8)
QTcF change >60 msec	1 (1.0)
QTcB outlier	
Any	37 (36.6)
New QTcB value >500 msec	0
New QTcB value >480 msec	3 (3.0)
New QTcB value >450 msec	23 (22.8)
QTcB change >30 to ≤60 msec	15 (14.9)
QTcB change >60 msec	0
Note: New is defined as not present at baseline but present on at least one post-baseline timepoint	
Source: CBGJ398X2204 CSR, Table 61; adae.xpt, adeg.xpt	

The Applicant's Position:

No cardiac toxicities related to Torsade de Pointes/QT prolongation were reported as TEAEs on study CBGJ398X2204. Median changes from baseline to maximum postbaseline were typically small for each ECG parameter: QT (30.0 msec), QTcF (17.0 msec), QTcB (18.0 msec), PR (13.3 msec), QRS (8.0 msec), and HR (11.0 msec). Formulation (FMI I or FMI III) had no appreciable effect on mean changes from baseline in the ECG parameters. Most subjects (85/101) evaluated for shifts from baseline in QTcF exhibited no shift from baseline to worst (maximum) postbaseline category. Fourteen subjects (13.9%) had a shift from ≤450 msec at baseline to >450 to 480 msec postbaseline, and 1 subject (1.0%) had a shift from >450 to 480 msec to >480

to 500 msec postbaseline. One subject (1.0%) had a shift from to >480 to 500 msec to ≤450 msec postbaseline. Similar results were generally observed for QTcB. No subjects had a newly occurring QTcF or QTcB value >500 msec at any postbaseline visit. No subjects had a newly-occurring QT, QTcF, or QTcB value >500 msec at any postbaseline visit. For QTcF, 14 subjects (13.9%) had a newly-occurring value >450 msec postbaseline, and 1 subject (1.0%) had a newly-occurring value >480 msec. Nineteen subjects (18.8%) had a change in QTcF from baseline to worst postbaseline between >30 to ≤60 msec; 1 subject (1.0%) had a change in QTcF from baseline to worst postbaseline ≥60 msec. Similar results were observed for QTcB. Three subjects (3.0%) had a >25% increase in PR from baseline to worst postbaseline with an absolute PR >200 msec, and 1 subject (1.0%) had a >25% increase in QRS from baseline to worst postbaseline with an absolute QRS >100 msec. Two subjects (2.0%) had a >25% decrease in HR from baseline to worst postbaseline with an absolute HR <50 bpm, and 7 subjects (6.9%) had a >25% increase in HR from baseline to worst postbaseline with an absolute HR >100 bpm.

The FDA's Assessment:

As summarized in the FDA QT-IRT Review Team review dated January 7, 2021, no large mean increases in the QTc interval (i.e., >20 msec) were observed in the QT assessment of 125 mg/day infigratinib (3-week-on-1 week-off dosing regimen); however, without a positive control or a large exposure margin, the FDA QT-IRT Review Team is reluctant to conclude a lack of an effect (ICH E14 Q&A (R3) 6.1). Therefore, FDA does not agree with the Applicant's conclusion in Section 6 that "infigratinib does not result in a clinically relevant (> 10 msec) mean increase in the QTc interval" given the lack of support from the submitted concentration-QT assessment. In addition, the QT assessment does not cover the increases in infigratinib exposure with concomitant use of strong CYP3A4 inhibitors, while there were concentration-dependent effects in the in vitro hERG study and in clinical studies.

The FDA QT-IRT Review Team states that there are no 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. The Truseltiq labeling has been revised to state that "at the recommended dosing regimen, infigratinib does not result in a large mean increase (i.e. >20 msec) in the QTc interval. The QT effect of infigratinib at higher exposures associated with CYP3A4 inhibition has not been studied".

In summary, no large effects on prolongation of the QT interval were identified during review of the data summarized above and information regarding higher exposures associated with CYP3A4 inhibition has been included in labeling. Please also refer to Sections 5.3 and 6.1.1 of

this review.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Ocular Disorder

The Applicant's Position:

Infigratinib, based on its mechanism of action, can cause Central Serous Retinopathy/Retinal Pigment Epithelial Detachment (CSR/RPED), which may cause symptoms such as blurred vision. All clinical trials of infigratinib conducted frequent routine ophthalmic monitoring to detect asymptomatic CSR/RPED. Among 351 patients who received infigratinib across clinical trials (125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set), CSR/RPED occurred in 11% of patients, including Grade 3 CSR/RPED in 0.9%. No Grade 4 CSR/RPED was observed. The median time to first onset of CSR/RPED was 26 days. CSR/RPED led to dose interruption/reduction of infigratinib in 3.4% of patients, and permanent discontinuation in 0.6 % of patients. Among 351 patients who received infigratinib across clinical trials, dry eye events occurred in 24% of patients, including Grade 3 in 0.3% of patients. No Grade 4 dry eye was observed.

The FDA's Assessment:

Because ocular toxicities are a class effect of FGFR inhibitors, an ophthalmology consult was obtained to assist with the assessment of ocular toxicities. Approximately 15% of patients experienced RPED, 21% had vision blurred, and 44% of patients experienced dry eye (in FDA analysis, using grouped preferred terms dry eye, keratitis, lacrimation increased, pinguecula, and punctate keratitis; these terms were grouped as there are alternative terms for an equivalent event). As stated in FDA's ophthalmology review, CTCAE grades are not considered reflective of the severity of ocular events and are not recommended to be used for these ocular events. Specifically, whether or not the RPED was resolving was more indicative, compared to CTCAE grade, of severity of injury and long-term sequelae and, thus, this approach was used in Section 2 of the USPI.

In the pooled safety population (351 patients receiving infigratinib at the indicated dose), CSR/RPED occurred in 11% of patients. The median time to first onset of CSR/RPED was 26 days and led to dose interruption/reduction of infigratinib in 3.4% of patients, and permanent

discontinuation in 0.6% of patients. Of note, the incidence of asymptomatic RPED is likely to be higher than the 15% reported on Study CBGJ398X2204 because not all patients had systematic monitoring with optical coherence tomography (OCT) (only 78% of patients had a post-baseline exam). Because ocular toxicity is an important risk for patients, Section 5.1 of the Truseltiq USPI states: “Perform a comprehensive ophthalmic examination including OCT prior to initiation of Truseltiq, 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 Truseltiq” This routine screening must be carried out in concert with ophthalmologists because the necessary procedures, such as OCT, are not generally performed outside of ophthalmology offices.

8.2.5.2 Hyperphosphatemia

The Applicant’s Position:

Increases in phosphate levels may occur as a pharmacodynamic effect of infigratinib. Among 351 patients who received infigratinib across clinical trials (125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set), hyperphosphatemia was reported in 82% of patients based on laboratory values above the upper limit of normal. The median time to onset of hyperphosphatemia was 8 days (range 1-349); median time to first onset of Grade 3 or Grade 4 hyperphosphatemia was 14.5 days (range: 7.0 to 43.0 days). Hyperphosphatemia was the only TEAE that led to dose reduction in $\geq 15\%$ of all subjects, with 25.9% of patients experiencing dose adjustment due to hyperphosphatemia. Phosphate-lowering therapy was received by 83% of patients who received infigratinib.

The FDA’s Assessment:

Hyperphosphatemia and related mineral metabolism issues are a class effect of FGFR inhibitors. Instructions for the management of hyperphosphatemia changed throughout the conduct of Study CBGJ398X2204. When the study was initiated, phosphate-binders were indicated prophylactically (i.e., in the absence of hyperphosphatemia). In amendment 1 (March 11, 2015), the study was revised to limit initiating of phosphate-binders to when serum phosphorus level was > 5.5 mg/dL. On the basis of an information request during the review of the NDA, the Applicant stated that a majority of patients (n=87; 81%) received a phosphate- while on study. Of these 87 patients, 52 (48%) initiated the phosphate-binder prophylactically. The extensive use of phosphate binders in Study CBGJ398X2204, including in the absence of hyperphosphatemia, significantly limited FDA’s ability to adequately assess the relationship between infigratinib and serum phosphate derangements; notably, the relatively high incidence of hypophosphatemia observed in this study is likely a direct effect of phosphate-binder therapy usage.

Irrespective of the timing and use of phosphate binders, hyperphosphatemia (89%), and hypophosphatemia (66%) were reported in the majority of patients; hypocalcemia was reported in 10% patients (data summarized in Table 46 and Table 48). Regarding specific

mineral metabolism-related clinical events in the 108-patient safety population, the following events were noted on FDA review of Cohort 1 of Study CBGJ398X2204:

- calcinosis/calciophylaxis 2.8% (3 patients)
- stress fracture 0.9% and compression fracture 0.9% (one patient, 2 events)
- myocardial calcification 0.9% (one patient)
- vascular calcification 0.9% (one patient)

Hyperphosphatemia generally does not cause symptoms unless there is precipitation of calcium-phosphate crystals leading to hypocalcemia; soft tissue mineralization, tetany, seizure activity, QT interval prolongation, and arrhythmias may result from effects on calcium, extra skeletal deposition of calcium phosphate crystals, and electrical hyperexcitability (Peppers et al 1991). A serious potential clinical sequelae of hyperphosphatemia of a Grade 3 bilateral peripheral arterial ischemia related to arterial calcification that lead to limbs amputations was reported in a different cohort of Study CBGJ398X2204.

Due to the prevalence of hyperphosphatemia with infigratinib and the need for early identification and intervention to avoid potential clinical sequelae, hyperphosphatemia is described in the Warnings and Precautions section of product labeling for infigratinib and management guidelines are included in the dosage modification table in Section 2.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Safety analyses by demographic subgroups for Study CBGJ398X2204 are summarized in Table 51 and Table 52 below.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 51: Overall Summary of Treatment-Emergent Adverse Events by Subgroup (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Category	Gender		Age		Region		CYP3A4 Inhibitors			CYP3A4 Inducers		All Subjects (N=108) n (%)
	Male (N=41) n (%)	Female (N=67) n (%)	<65 years (N=82) n (%)	≥65 years (N=26) n (%)	North America (N=77) n (%)	Western Europe (N=24) n (%)	Used Strong Inhibitor (N=20) n (%)	Used Moderate Inhibitor (N=15) n (%)	Did Not Use Inhibitor (N=73) n (%)	Used Strong Inducer (N=17) n (%)	Did Not Use Inducer (N=91) n (%)	
Any TEAE	41 (100.0)	66 (98.5)	81 (98.8)	26 (100.0)	76 (98.7)	24 (100)	20 (100.0)	15 (100.0)	72 (98.6)	17 (100.0)	90 (98.9)	107 (99.1)
AE outcome fatal	0	1 (1.5)	0	1 (3.8)	0	0	1 (5.0)	0	0	1 (5.9)	0	1 (0.9)
Treatment-related TEAE	38 (92.7)	66 (98.5)	79 (96.3)	25 (96.2)	75 (97.4)	22 (91.7)	20 (100.0)	15 (100.0)	69 (94.5)	16 (94.1)	88 (96.7)	104 (96.3)
Serious TEAE (SAE)	11 (26.8)	23 (34.3)	25 (30.5)	9 (34.6)	24 (31.2)	7 (29.2)	8 (40.0)	7 (46.7)	19 (26.0)	7 (41.2)	27 (29.7)	34 (31.5)
Serious Treatment-related TEAE	3 (7.3)	6 (9.0)	6 (7.3)	3 (11.5)	7 (9.1)	1 (4.2)	2 (10.0)	1 (6.7)	6 (8.2)	1 (5.9)	8 (8.8)	9 (8.3)
Grade 3 or 4 TEAE	27 (65.9)	43 (64.2)	50 (61.0)	20 (76.9)	54 (70.1)	12 (50.0)	16 (80.0)	11 (73.3)	43 (58.9)	10 (58.8)	60 (65.9)	70 (64.8)
TEAE leading to dose interruption	23 (56.1)	46 (68.7)	50 (61.0)	19 (73.1)	49 (63.6)	15 (62.5)	16 (80.0)	12 (80.0)	41 (56.2)	13 (76.5)	56 (61.5)	69 (63.9)
TEAE leading to dose adjustment	20 (48.8)	45 (67.2)	48 (58.5)	17 (65.4)	52 (67.5)	9 (37.5)	15 (75.0)	11 (73.3)	39 (53.4)	11 (64.7)	54 (59.3)	65 (60.2)
TEAE requiring concomitant medication or non-drug therapy	38 (92.7)	65 (97.0)	77 (93.9)	26 (100.0)	75 (97.4)	22 (91.7)	20 (100.0)	15 (100.0)	68 (93.2)	17 (100.0)	86 (94.5)	103 (95.4)
TEAE leading to treatment discontinuation	11 (26.8)	5 (7.5)	10 (12.2)	6 (23.1)	11 (14.3)	2 (8.3)	2 (10.0)	2 (13.3)	12 (16.4)	3 (17.6)	13 (14.3)	16 (14.8)
Abbreviations: AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event. Source: CBGJ398X2204 CSR, Table 34 adae.xpt												

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 52: Treatment Emergent Adverse Events Occurring in ≥10% of All Subjects by Preferred Term and Subgroup (Study CBGJ398X2204 Interim Analysis Set 2 for Cohort 1)

Preferred Term	Gender		Age		Region		CYP3A4 Inhibitors			CYP3A4 Inducers		All Subjects (N=108) n (%)
	Male (N=41) n (%)	Female (N=67) n (%)	<65 years (N=82) n (%)	≥65 years (N=26) n (%)	North America (N=77) n (%)	Western Europe (N=24) n (%)	Used Strong Inhibitor (N=20) n (%)	Used Moderate Inhibitor (N=15) n (%)	Did Not Use Inhibitor (N=73) n (%)	Used Strong Inducer (N=17) n (%)	Did Not Use Inducer (N=91) n (%)	
Hyperphosphataemia	30 (73.2)	53 (79.1)	66 (80.5)	17 (65.4)	62 (80.5)	15 (62.5)	16 (80.0)	11 (73.3)	56 (76.7)	14 (82.4)	69 (75.8)	83 (76.9)
Stomatitis	18 (43.9)	41 (61.2)	43 (52.4)	16 (61.5)	45 (58.4)	10 (41.7)	14 (70.0)	12 (80.0)	33 (45.2)	13 (76.5)	46 (50.5)	59 (54.6)
Fatigue	12 (29.3)	31 (46.3)	33 (40.2)	10 (38.5)	34 (44.2)	5 (20.8)	11 (55.0)	7 (46.7)	25 (34.2)	7 (41.2)	36 (39.6)	43 (39.8)
Alopecia	15 (36.6)	26 (38.8)	37 (45.1)	4 (15.4)	31 (40.3)	9 (37.5)	8 (40.0)	6 (40.0)	27 (37.0)	6 (35.3)	35 (38.5)	41 (38.0)
Dry eye	9 (22.0)	28 (41.8)	31 (37.8)	6 (23.1)	30 (39.0)	6 (25.0)	10 (50.0)	5 (33.3)	22 (30.1)	6 (35.3)	31 (34.1)	37 (34.3)
Palmar-plantar erythrodysesthesia syndrome	13 (31.7)	23 (34.3)	28 (34.1)	8 (30.8)	30 (39.0)	4 (16.7)	6 (30.0)	8 (53.3)	22 (30.1)	9 (52.9)	27 (29.7)	36 (33.3)
Arthralgia	11 (26.8)	23 (34.3)	25 (30.5)	9 (34.6)	31 (40.3)	2 (8.3)	8 (40.0)	5 (33.3)	21 (28.8)	6 (35.3)	28 (30.8)	34 (31.5)
Dysgeusia	15 (36.6)	19 (28.4)	27 (32.9)	7 (26.9)	28 (36.4)	4 (16.7)	10 (50.0)	5 (33.3)	19 (26.0)	5 (29.4)	29 (31.9)	34 (31.5)
Constipation	14 (34.1)	18 (26.9)	23 (28.0)	9 (34.6)	23 (29.9)	7 (29.2)	8 (40.0)	5 (33.3)	19 (26.0)	6 (35.3)	26 (28.6)	32 (29.6)
Dry mouth	8 (19.5)	19 (28.4)	21 (25.6)	6 (23.1)	23 (29.9)	4 (16.7)	9 (45.0)	4 (26.7)	14 (19.2)	3 (17.6)	24 (26.4)	27 (25.0)
Hypercalcaemia	7 (17.1)	20 (29.9)	22 (26.8)	5 (19.2)	21 (27.3)	6 (25.0)	5 (25.0)	5 (33.3)	17 (23.3)	5 (29.4)	22 (24.2)	27 (25.0)
Blood creatinine increased	12 (29.3)	14 (20.9)	19 (23.2)	7 (26.9)	19 (24.7)	7 (29.2)	5 (25.0)	3 (20.0)	18 (24.7)	3 (17.6)	23 (25.3)	26 (24.1)
Diarrhoea	7 (17.1)	19 (28.4)	18 (22.0)	8 (30.8)	15 (19.5)	8 (33.3)	11 (55.0)	1 (6.7)	14 (19.2)	1 (5.9)	25 (27.5)	26 (24.1)
Dry skin	9 (22.0)	16 (23.9)	21 (25.6)	4 (15.4)	21 (27.3)	3 (12.5)	8 (40.0)	1 (6.7)	16 (21.9)	3 (17.6)	22 (24.2)	25 (23.1)
Decreased appetite	10 (24.4)	14 (20.9)	18 (22.0)	6 (23.1)	19 (24.7)	3 (12.5)	8 (40.0)	6 (40.0)	10 (13.7)	6 (35.3)	18 (19.8)	24 (22.2)
Hypophosphataemia	9 (22.0)	15 (22.4)	22 (26.8)	2 (7.7)	19 (24.7)	3 (12.5)	5 (25.0)	5 (33.3)	14 (19.2)	4 (23.5)	20 (22.0)	24 (22.2)
Aspartate aminotransferase increased	9 (22.0)	14 (20.9)	19 (23.2)	4 (15.4)	18 (23.4)	4 (16.7)	4 (20.0)	3 (20.0)	16 (21.9)	7 (41.2)	16 (17.6)	23 (21.3)
Vision blurred	7 (17.1)	16 (23.9)	18 (22.0)	5 (19.2)	22 (28.6)	0	8 (40.0)	2 (13.3)	13 (17.8)	5 (29.4)	18 (19.8)	23 (21.3)
Vomiting	5 (12.2)	18 (26.9)	17 (20.7)	6 (23.1)	21 (27.3)	2 (8.3)	8 (40.0)	5 (33.3)	10 (13.7)	4 (23.5)	19 (20.9)	23 (21.3)
Anaemia	8 (19.5)	12 (17.9)	18 (22.0)	2 (7.7)	18 (23.4)	0	5 (25.0)	6 (40.0)	9 (12.3)	5 (29.4)	15 (16.5)	20 (18.5)
Nausea	6 (14.6)	14 (20.9)	13 (15.9)	7 (26.9)	18 (23.4)	2 (8.3)	5 (25.0)	5 (33.3)	10 (13.7)	3 (17.6)	17 (18.7)	20 (18.5)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Preferred Term	Gender		Age		Region		CYP3A4 Inhibitors			CYP3A4 Inducers		All Subjects (N=108) n (%)
	Male (N=41) n (%)	Female (N=67) n (%)	<65 years (N=82) n (%)	≥65 years (N=26) n (%)	North America (N=77) n (%)	Western Europe (N=24) n (%)	Used Strong Inhibitor (N=20) n (%)	Used Moderate Inhibitor (N=15) n (%)	Did Not Use Inhibitor (N=73) n (%)	Used Strong Inducer (N=17) n (%)	Did Not Use Inducer (N=91) n (%)	
Epistaxis	7 (17.1)	12 (17.9)	16 (19.5)	3 (11.5)	18 (23.4)	1 (4.2)	3 (15.0)	2 (13.3)	14 (19.2)	6 (35.3)	13 (14.3)	19 (17.6)
Nail discolouration	8 (19.5)	11 (16.4)	16 (19.5)	3 (11.5)	18 (23.4)	0	2 (10.0)	4 (26.7)	13 (17.8)	6 (35.3)	13 (14.3)	19 (17.6)
Abdominal pain	8 (19.5)	10 (14.9)	12 (14.6)	6 (23.1)	13 (16.9)	4 (16.7)	4 (20.0)	4 (26.7)	10 (13.7)	5 (29.4)	13 (14.3)	18 (16.7)
Dyspepsia	7 (17.1)	11 (16.4)	14 (17.1)	4 (15.4)	14 (18.2)	4 (16.7)	4 (20.0)	3 (20.0)	11 (15.1)	4 (23.5)	14 (15.4)	18 (16.7)
Headache	4 (9.8)	14 (20.9)	15 (18.3)	3 (11.5)	13 (16.9)	4 (16.7)	6 (30.0)	2 (13.3)	10 (13.7)	4 (23.5)	14 (15.4)	18 (16.7)
Pain in extremity	7 (17.1)	11 (16.4)	13 (15.9)	5 (19.2)	16 (20.8)	2 (8.3)	5 (25.0)	2 (13.3)	11 (15.1)	5 (29.4)	13 (14.3)	18 (16.7)
Onychomadesis	10 (24.4)	7 (10.4)	14 (17.1)	3 (11.5)	15 (19.5)	1 (4.2)	4 (20.0)	3 (20.0)	10 (13.7)	2 (11.8)	15 (16.5)	17 (15.7)
Alanine aminotransferase increased	6 (14.6)	10 (14.9)	14 (17.1)	2 (7.7)	13 (16.9)	3 (12.5)	3 (15.0)	3 (20.0)	10 (13.7)	4 (23.5)	12 (13.2)	16 (14.8)
Blood alkaline phosphatase increased	7 (17.1)	9 (13.4)	14 (17.1)	2 (7.7)	12 (15.6)	2 (8.3)	4 (20.0)	3 (20.0)	9 (12.3)	3 (17.6)	13 (14.3)	16 (14.8)
Nail disorder	8 (19.5)	8 (11.9)	12 (14.6)	4 (15.4)	11 (14.3)	5 (20.8)	2 (10.0)	2 (13.3)	12 (16.4)	4 (23.5)	12 (13.2)	16 (14.8)
Pyrexia	4 (9.8)	12 (17.9)	14 (17.1)	2 (7.7)	13 (16.9)	2 (8.3)	5 (25.0)	4 (26.7)	7 (9.6)	6 (35.3)	10 (11.0)	16 (14.8)
Weight decreased	4 (9.8)	12 (17.9)	11 (13.4)	5 (19.2)	14 (18.2)	0	5 (25.0)	6 (40.0)	5 (6.8)	3 (17.6)	13 (14.3)	16 (14.8)
Back pain	3 (7.3)	12 (17.9)	11 (13.4)	4 (15.4)	9 (11.7)	5 (20.8)	5 (25.0)	4 (26.7)	6 (8.2)	6 (35.3)	9 (9.9)	15 (13.9)
Abdominal pain upper	4 (9.8)	10 (14.9)	10 (12.2)	4 (15.4)	11 (14.3)	2 (8.3)	5 (25.0)	1 (6.7)	8 (11.0)	2 (11.8)	12 (13.2)	14 (13.0)
Hyponatraemia	4 (9.8)	10 (14.9)	11 (13.4)	3 (11.5)	12 (15.6)	1 (4.2)	3 (15.0)	2 (13.3)	9 (12.3)	3 (17.6)	11 (12.1)	14 (13.0)
Insomnia	6 (14.6)	8 (11.9)	12 (14.6)	2 (7.7)	11 (14.3)	1 (4.2)	3 (15.0)	3 (20.0)	8 (11.0)	4 (23.5)	10 (11.0)	14 (13.0)
Myalgia	2 (4.9)	12 (17.9)	12 (14.6)	2 (7.7)	13 (16.9)	1 (4.2)	3 (15.0)	2 (13.3)	9 (12.3)	3 (17.6)	11 (12.1)	14 (13.0)
Oedema peripheral	6 (14.6)	8 (11.9)	12 (14.6)	2 (7.7)	12 (15.6)	1 (4.2)	3 (15.0)	3 (20.0)	8 (11.0)	5 (29.4)	9 (9.9)	14 (13.0)
Onychalgia	5 (12.2)	9 (13.4)	10 (12.2)	4 (15.4)	13 (16.9)	1 (4.2)	3 (15.0)	2 (13.3)	9 (12.3)	6 (35.3)	8 (8.8)	14 (13.0)
Cough	7 (17.1)	6 (9.0)	10 (12.2)	3 (11.5)	11 (14.3)	1 (4.2)	4 (20.0)	5 (33.3)	4 (5.5)	1 (5.9)	12 (13.2)	13 (12.0)
Lacrimation increased	6 (14.6)	7 (10.4)	9 (11.0)	4 (15.4)	12 (15.6)	1 (4.2)	2 (10.0)	0	11 (15.1)	3 (17.6)	10 (11.0)	13 (12.0)
Onycholysis	4 (9.8)	9 (13.4)	12 (14.6)	1 (3.8)	9 (11.7)	3 (12.5)	1 (5.0)	3 (20.0)	9 (12.3)	4 (23.5)	9 (9.9)	13 (12.0)
Blepharitis	3 (7.3)	9 (13.4)	9 (11.0)	3 (11.5)	8 (10.4)	3 (12.5)	2 (10.0)	2 (13.3)	8 (11.0)	3 (17.6)	9 (9.9)	12 (11.1)
Lipase increased	6 (14.6)	6 (9.0)	10 (12.2)	2 (7.7)	9 (11.7)	2 (8.3)	4 (20.0)	1 (6.7)	7 (9.6)	0	12 (13.2)	12 (11.1)
Trichiasis	6 (14.6)	6 (9.0)	8 (9.8)	4 (15.4)	10 (13.0)	1 (4.2)	3 (15.0)	1 (6.7)	8 (11.0)	4 (23.5)	8 (8.8)	12 (11.1)

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

	Gender		Age		Region		CYP3A4 Inhibitors			CYP3A4 Inducers		All Subjects (N=108) n (%)
	Male (N=41) n (%)	Female (N=67) n (%)	<65 years (N=82) n (%)	≥65 years (N=26) n (%)	North America (N=77) n (%)	Western Europe (N=24) n (%)	Used Strong Inhibitor (N=20) n (%)	Used Moderate Inhibitor (N=15) n (%)	Did Not Use Inhibitor (N=73) n (%)	Used Strong Inducer (N=17) n (%)	Did Not Use Inducer (N=91) n (%)	
Preferred Term												
Note: Events are listed by descending order of incidence in the All Subjects column; terms with the same incidence are presented in alphabetical order. Source: CBGJ398X2204 CSR, Table 35; adae.xpt												

The Applicant's Position:

Subgroup analyses of TEAEs and SAEs by gender, age, region, and CYP3A4 inducers and inhibitors were conducted and did not reveal any clinically relevant trends or patterns.

The FDA's Assessment:

No obvious differences are seen when gender and age subgroups are examined based on the table, above. However, because Study CBGJ398X2204 was not powered to observe differences among these subgroups, definitive conclusions cannot be made.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Carcinogenicity studies have not been conducted with infigratinib and are not required to support the use of infigratinib in the proposed indication.

The FDA's Assessment:

N/A

Human Reproduction and Pregnancy

The Applicant's Position:

There are no clinical data on the use of infigratinib in pregnant women. There were no pregnancies or lactation events reported in the infigratinib clinical development program.

Embryo-fetal development studies investigating the administration of infigratinib during the period of organogenesis were conducted in rats and rabbits. In rats, infigratinib administration resulted in an increase in embryo-fetal lethality at 10 mg/kg/day, and reductions in fetal body

weights at 3 and 10 mg/kg/day. Fetal abnormalities (external, soft tissue, and skeletal) were increased at ≥ 1 mg/kg/day (maternal exposures at all dose levels less than the human exposure (AUC) at the maximum recommended human dose). In rabbits, infigratinib administration resulted in reductions in fetal body weights at 3 mg/kg/day, which was considered to be a maternally toxic dose (maternal exposures at all dose levels less than the human exposure (AUC) at the maximum recommended human dose). Correlated with the reduction in fetal weights was a decrease in the numbers of ossification sites in some bones.

The FDA's Assessment:

The USPI will reflect that infigratinib has not been studied in pregnant or lactating women and that, based on animal studies and its mechanism of action, it can cause fetal harm. Contraception is advised for woman and men for the duration of treatment and for 1 month after the final dose.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable.

The FDA's Assessment:

N/A. No pediatric patients were enrolled in the CBGJ398X2204 trial.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no specific antidote for an infigratinib overdose, and the benefit of hemodialysis is unknown. In the event of an overdose, infigratinib administration should be withheld and general supportive measures undertaken. Infigratinib is self-administered orally by the patient. There is a low potential for intentional overdose. No cases of infigratinib overdose >125 mg were reported as AEs in clinical trials. The potential for accidental overdose is low because infigratinib will be prescribed by a physician and dispensed by a licensed pharmacist in 21-day dose packs. Infigratinib capsules are available as a 25 mg capsule with a white opaque body and gray opaque cap imprinted with INFI 25mg on the body, and as a 100 mg capsule with a white opaque body and light orange cap imprinted with INFI 100mg on the body. Each potential dose level (125, 100, 75, or 50 mg QD) is provided in a preconfigured blister pack that contains the correct number of capsules for the indicated daily dose.

It is not foreseen that infigratinib has drug abuse potential. Nonclinical pharmacokinetic studies in rats do show that infigratinib crosses the blood brain barrier. However, animal studies with repeated dosing do not support an ability of the drug to induce general behavioral

changes, and review of humans TEAE data concur the lack of findings.

Withdrawal of infigratinib will most often lead to reversal of or improvements in on target effects, such as hyperphosphatemia. A rebound effect was not noted.

The FDA's Assessment:

FDA generally agrees with the Applicant's statement above.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable; infigratinib has not yet been marketed in any country.

The FDA's Assessment:

N/A

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities appear to have been adequately represented and characterized in CBGJ398X2204 study. Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

Routine pharmacovigilance will be important to monitor for expected toxicities (including mineral-metabolism and ocular issues) and to monitor for any unexpected adverse events. The review team determined that a REMS is not required to ensure safe and effective use of infigratinib. Infigratinib will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The overall safety review is focused on data from the primary safety analysis set (108 subjects with cholangiocarcinoma from study CBGJ398X2204; median exposure of 5.52 months) and the 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set (351 subjects with advanced cancer from Studies CBGJ398X2101, CBGJ398X2201, CBGJ398XUS04, and

CBGJ398X2204 [Cohorts 1-3]; median exposure of 3.06 months). In both analysis sets, subjects received infigratinib monotherapy on the 125 mg 3 weeks on/1 week off schedule. Unless otherwise noted, this discussion focuses on the integrated 125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set.

The demographic profile of patients in study CBGJ398X2204 is broadly representative of the population described in the proposed indication of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement as detected by a validated test. In general, the AEs observed with infigratinib were consistent with its mechanism of action, ie, FGFR inhibition, and the toxicity profile observed in nonclinical studies. The important identified risks related to infigratinib are ocular toxicity (including CSR/RPED) and hyperphosphatemia.

Ocular toxicity (including CSR/RPED), an on-target effect of infigratinib, was monitored in studies by scheduled ophthalmology assessments. Ophthalmic assessments were scheduled frequently in the Phase 1 dose-finding Study CBGJ398X2101 (weekly for months 1 and 2 and then on Days 1 and 15 of subsequent cycles); monthly after Month 1 in Studies CBGJ398X2201 and CBGJ398XUS04; and, in Study CBGJ398X2204, on Days 1 and 15 of Month 1; monthly for Months 2 3; and then every 4 months. OCT examinations were generally not required in the monotherapy safety analysis set but were introduced with Amendment 4 of Study CBGJ398X2204 (April 2019).

Overall, ocular toxicity was reported in 52.7% of subjects. The most commonly reported AEs were dry eye and blurred vision. The median time to onset was 23 days for any eye disorder AE (88 days for Grade 3 or 4). Eye disorder AEs were often considered related to study drug, which consequently led to treatment with concomitant medications or nondrug therapy or, less frequently, dose modifications. Many eye disorder AEs were not considered recovered or resolved at the time of last subject record. No Grade 4 CSR/RPED AESI was reported. Because ocular toxicity is a clinically significant risk, product labeling should warn about the adverse reaction of ocular disorder and will include a recommended schedule for comprehensive ophthalmic examinations, including OCT, and guidance to use demulcents as indicated.

Hyperphosphatemia, another on-target effect of infigratinib, was monitored in studies by scheduled chemistry assessments. Chemistry assessments were performed frequently in Studies CBGJ398X2101, CBGJ398X2201, and CBGJ398XUS04 (several times in Month 1 and then twice a month for subsequent cycles); in Study CBGJ398X2204, chemistries were assessed on Days 1, 8, 15, and 21 of Month 1; Days 1 and 15 of Month 2; and then monthly thereafter. In Study CBGJ398X2101, prophylactic phosphate lowering therapy and dietary phosphate restriction were recommended after the maximum tolerated dose was established. This management strategy was subsequently implemented in Studies CBGJ398X2201, CBGJ398XUS04, and CBGJ398X2204. Hyperphosphatemia was reported in 70.9% of subjects as an AESI. The median onset was 8 days (15 days for Grade 3 or 4); AEs were generally Grade 1 or

2, led to dose modifications, required treatment with concomitant medications or nondrug therapy, and generally resolved/recovered. There were 2 SAEs of hyperphosphatemia. Because hyperphosphatemia is a clinically significant risk, product labeling should warn about the adverse reaction of hyperphosphatemia and includes a recommended schedule for laboratory monitoring and guidance regarding phosphate-lowering therapy (b) (4)

No clinically meaningful safety differences were identified between infigratinib formulations.

Most subjects (99.1%) had an AE on study; the most common ($\geq 35\%$) were hyperphosphatemia (64.4%), fatigue (43.6%), stomatitis (37.6%), and constipation (35.0%). Grade 3 or 4 AEs were reported for 64.7% of subjects; most were due to abnormal laboratory findings. AEs leading to study drug discontinuation occurred in 14.0% of subjects, most commonly due to increased blood creatinine (1.4%). To convey a clinically meaningful safety profile in the adverse reactions section of the proposed infigratinib label, AEs with similar medical concepts in the primary safety analysis set were grouped, and an appropriate cut-off ($\geq 15\%$ of subjects) was established.

Of the 63.0% of subjects who died during a study, most (202 of 221) died due to the study indication. Nonfatal SAEs were reported for 37.0% of subjects. The most commonly reported SAEs ($\sim 3\%$ of subjects) were pyrexia, sepsis, and anemia. Overall, these SAEs could be attributed to underlying disease or an infection.

No drug-induced liver injury/true Hy's Law cases were identified based on the case series analysis performed.

Overall, the adverse reactions observed with infigratinib were consistent with its mechanism of action and the toxicity observed in nonclinical studies. The important identified risks related to infigratinib are ocular toxicity (including CSR/RPED) and hyperphosphatemia. These risks can be managed by oncologists with routine laboratory monitoring and ophthalmic assessments, dose interruptions or reductions, and concomitant medications or nondrug therapies. The safety risks of infigratinib seem acceptable when the benefits of the observed antitumor effects are considered in a patient population with a serious and life-threatening condition.

The FDA's Assessment:

The "125 mg 3 weeks on/1 week off schedule monotherapy safety analysis set", consisting of 351 patients who received infigratinib at the to be prescribed dosage who enrolled into clinical studies CBGJ398X2101, CBGJ398X2201, CBGJ398X2204 (Cohorts 1-3), and CBGJ398XUS04 is adequate to characterize the safety of infigratinib.

In general, the adverse reactions observed with infigratinib were consistent

with the mechanism of action and toxicity observed in preclinical studies of infigratinib. The primary risks related to infigratinib are hyperphosphatemia and ocular toxicities including RPED, dry eye, and vision blurred. The actual incidences of ocular toxicity and hyperphosphatemia/hypophosphatemia are confounded by missing OCT exams and by the prophylactic use of phosphate-binders. These serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of infigratinib product labeling and will additionally be monitored in patients through post-marketing pharmacovigilance efforts. The major safety risks of infigratinib are toxicities that oncologists frequently manage and the toxicity profile of infigratinib is considered acceptable when considering the anti-tumor effects observed (e.g., durable responses) in a patient population with a serious and life-threatening condition.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues in the review of this NDA. FDA does not consider inferential procedures in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response, compared with the available therapies at time of approval. Results of time-to-event endpoints such as PFS and OS were not interpretable without a control.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The primary efficacy results of Study CBGJ398X2204, based upon data from 108 patients with cholangiocarcinoma harboring a FGFR2 gene fusion or other rearrangement (Cohort 1), demonstrate that treatment with infigratinib results in clinically meaningful responses that are durable in patients with previously treated unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement, a serious and life threatening disease. The response rate (BICR-assessed confirmed ORR according to RECIST 1.1) of 23.1% (95%: 15.6, 32.2) with a median duration of response of 5.03 months (95% CI: 3.71, 9.26) can be considered meaningful, given that life expectancy in this setting is 5-6 months. Although pemigatinib is approved for the same indication, pemigatinib was approved under the accelerated approval regulations and therefore cannot be considered available therapy. There are no other available FDA-approved drugs for the second-line treatment of patients with unresectable or metastatic cholangiocarcinoma.

The safety review consisted of data from 351 adult patients from 4 single-arm trials, studies

CBGJ398X2101, CBGJ398X2201, CBGJ398X2204 (Cohorts 1-3), and CBGJ398XUS04 and primarily focused on Cohort 1 of Study CBGJ398X2204. In general, the adverse reactions observed with infigratinib were consistent with the mechanism of action and toxicity observed in preclinical studies of infigratinib. The primary risks related to infigratinib are hyperphosphatemia and ocular toxicities including RPED, dry eye, and blurred vision. The most common adverse events (incidence $\geq 20\%$) in patients with unresectable or metastatic, FGFR-mutated cholangiocarcinoma included nail toxicity, stomatitis, dry eye, fatigue, alopecia, palmar-plantar erythrodysesthesia syndrome, arthralgia, dysgeusia, constipation, abdominal pain, dry mouth, eyelash changes, diarrhea, dry skin, decreased appetite, vision blurred and vomiting. The most common relevant laboratory abnormalities were increased creatinine, increased phosphate, decreased phosphate, decreased hemoglobin, and increased calcium.

Key review issues considered during review of this application included:

1. Inadequate justification of the proposed dosage of 125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles. Selection of the recommended dose was based on the MTD of the first-in-human dose escalation/dose expansion Study CBGJ398X2101. Acknowledging the exploratory nature of the analyses, in FDA's review, the exposure-efficacy relationship suggests that an alternative lower dosage may provide similar efficacy, supported by a positive exposure-relationship reported by hyperphosphatemia. In addition, the high rate of dosing modifications (interruptions and dose decrease) and high rate of early dose modifications (Cycles 1 and 2) suggests that the current dosage is not well tolerated, and further dosage evaluations are needed. A PMR (see below) to address this issue was negotiated during the review cycle.
2. The extent of RPED was confounded by lack of routine OCT examinations in most patients. RPED can be asymptomatic and because of monitoring issues, these asymptomatic cases were likely not captured in the safety database.
3. The assessment of hyperphosphatemia, confounded by the prophylactic use of phosphate-binders and changes in the protocol instructions for the management/prevention of hyperphosphatemia.

The serious risks of eye toxicity and hyperphosphatemia are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of infigratinib product labeling. The major safety risks of infigratinib are toxicities that oncologists frequently manage in consultation with ophthalmologists and the toxicity profile of infigratinib is considered acceptable when considering the anti-tumor effects observed (e.g., durable responses in 23% of patients) in a patient population with a serious and life-threatening condition.

The review team concludes that overall, the results of Study CBJ398X2204 are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and represent a meaningful advantage over existing treatments for the proposed indication, meeting the requirements for accelerated approval. As a condition of accelerated approval, a post marketing study will be required to confirm the benefit of infigratinib.

X

X

Abhishek Bhattacharjee
Primary Statistical Reviewer

Joyce Cheng
Statistical Team Leader

X

X

Lorraine Pelosof
Primary Clinical Reviewer

Sandra J. Casak
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this NDA because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of infigratinib for the proposed indication. Infigratinib is the third in-class product reviewed by FDA for the treatment of cancer and the second one for the treatment of FGFR2-mutated cholangiocarcinoma.

10 Pediatrics

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Infigratinib was granted Orphan Designation on September 11, 2019 for the treatment of cholangiocarcinoma and in accordance with 21 CFR 314.55(5)(d), orphan drugs are exempt from the pediatric study requirements under 21 CFR 314.55.

To fulfill the pediatric requirements in Section 505B of the FD&C Act as amended by Title V of FDARA regarding pediatric evaluation of certain molecularly targeted oncology drugs, QED Therapeutics submitted a pediatric study plan (PSP) that includes a clinical study in patients 29 days of age old or older with FGFR-altered tumors. This 2-part study will determine the recommended Phase 2 dose of infigratinib in pediatric patients with recurrent or refractory low grade glioma and other advanced solid tumors with disease progression after at least 1 prior standard therapy appropriate for tumor type and stage of disease unless available standard therapies are considered inadequate for the subject harboring fibroblast growth factor receptor FGFR1, FGFR2, or FGFR3 alterations and will also assess safety and PK. In Part 2, the antitumor activity of infigratinib will be assessed in patients with low-grade glioma with recurrent or refractory disease harboring selected FGFR1, FGFR2, or FGFR3 alterations. FDA issued a written response acknowledging QED's amended Agreed initial Pediatric Study Plan submitted on September 24, 2020. A deferral for the submission of results of pediatric studies in pediatric patients 29 days of age or older is requested with this NDA submission as the planned study has not been initiated. FDA agrees with this request and a PMR for the submission of the pediatric study results was agreed.

A request for a partial waiver for the conduct of a molecularly targeted investigation in neonates (newborns to 28 day old) is requested, given FGFR1-3 genetically altered, refractory solid tumors occur so rarely in this age group that studies would be impossible or highly impractical. FDA agrees with this request.

11 Labeling Recommendations

Table 53 summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for TRUSELTIQ (infigratinib capsules) accompanying the approval letter for more information.

Table 53: Summary of Significant Labeling Changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
DOSAGE AND ADMINISTRATION	TRUSELTIQ dosage modifications for the adverse reactions hyperphosphatemia and serous retinal detachment were described.	TRUSELTIQ dose reductions and dosage modifications for adverse reactions were revised. In addition, the adverse reaction, “(b) (4)” was revised to “retinal pigment epithelial detachment (RPED)” and TRUSELTIQ dosage modification recommendations for this adverse reaction were revised for clarity. Addition of instructions (Subsections 2.4, 2.5, and 2.6) for dosage modification for concomitant use of gastric acid reducing agents, dosage modification for mild and severe renal and hepatic impairment.
WARNINGS AND PRECAUTIONS	5.1 (b) (4)	Revised to: “5.1 Ocular Toxicity” because the body of the warning and precaution was revised to discuss not only retinal pigment epithelial detachment or RPED (revised term from “(b) (4)” to more adequately describe the adverse reaction) but also dry eye as well. Although the incidence of RPED observed across clinical trials was noted, a statement

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

		was also including stating that clinical trials of TRUSELTRIQ did not conduct routine monitoring including optical coherence tomography (OCT) to detect asymptomatic RPED.
WARNINGS AND PRECAUTIONS	5.2 Hyperphosphatemia	Revised to: “5.2 Hyperphosphatemia and Soft Tissue Mineralization” to reflect the observed effect of secondary hypercalcemia on soft tissues.
ADVERSE REACTIONS/ Clinical Trials Experience		(b) (4) insertion of a dedicated table for lab abnormalities. Addition of statement informing of the incidence of pathological fractures.
USE IN SPECIFIC POPULATIONS	Sections 8.6.and 8.7	Addition of subsections with recommendations for TRUSELTIQ dosage in patients with mild and moderate renal and hepatic impairment respectively.
CLINICAL PHARMACOLOGY	Section 12.3	Addition of subsections with PK data in patients with mild and moderate renal and hepatic impairment respectively.
CLINICAL STUDIES	Section 14.1	Deletion of table (b) (4).

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of infigratinib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of infigratinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

QED agreed to the following clinical postmarketing requirements (PMR) and commitments (PMC):

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

PMR #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.

PMR #3:

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 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.

PMR #4:

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.”

PMR #5:

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.”

PMR #6:

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.”

PMR #7:

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.”

PMR #8:

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.”

PMC #1:

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.”

PMC #2:

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.

14 Division Director (DHOT) (NME ONLY)

X

John Leighton

15 Division Director (OCP)

X

NAM Atiqur Rahman

16 Division Director (OB)

X

Shenghui Tang

17 Division Director (Clinical)

X

'Lola Fashoyin-Aje

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Paul Kluetz

19 Appendices

19.1. References

The Applicant's References:

Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020 Jun;21(6):796-807.

Alpini G, McGill JM, Larusso NF. The pathobiology of biliary epithelia. *Hepatology.* 2002;35(5):1256–1268

American Cancer Society. Key Statistics for Bile Duct Cancer. 03 July 2018.
<https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html>. Accessed 03 June 2020.

Arai Y, Totoki Y, Hosoda F, Shiota T, Hama N, Nakamura H, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. *Hepatology.* 2014;59(4):1427–1434.

Babina IS, Turner NC. Advances and challenges in targeting FGFR signaling in cancer. *Nat Rev Cancer.* 2017;17(5):318–332.

Blechacz B. Cholangiocarcinoma: current knowledge and new developments. *Gut Liver.* 2017;11(1):13–26.

Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol.* 2014;60(6):1268–1289.

Caparica R, Lengelé A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. *Autops Case Rep.* 2019;9(2):e2019087.
<https://doi.org/10.4322/acr.2019.087>

Churi CR, Shroff R, Wang Y, Rashid A, Kang HC, Weatherly J, et al. Mutation profiling in cholangiocarcinoma: prognostic and therapeutic implications. *PLoS One.* 2014;9(12):e115383.
[doi:10.1371/journal.pone.0115383](https://doi.org/10.1371/journal.pone.0115383).

Dana-Farber Cancer Institute. Biliary Cancer. <https://www.dana-farber.org/biliary-cancer/about/>. Accessed 03 June 2020.

Di Stefano AL, Fucci A, Frattini V, Labussiere M, Mokhtari K, Zoppoli P, et al. Detection, characterization, and inhibition of FGFR-TACC fusions in IDH wild-type glioma. Clin Cancer Res. 2015;21(14):3307-3317.

Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. Gastroenterology. 2009;136(4):1134–1144.

Farshidfar F, Zheng S, Gingras M-C, Newton Y, Shih J, Robertson AG, et al. Integrative genomic analysis of cholangiocarcinoma identifies distinct IDH-mutant molecular profiles. Cell Rep. 2017;18(11):2780–2794. Correction in: Cell Rep. 2017;19(13):2878–2880.

Ghouri YA, Mian I, Blechacz B. Cancer review: Cholangiocarcinoma. J Carcinog. 2015;14:1. doi:10.4103/1477-3163.151940.

Goeppert B, Roessler S, Renner M, Singer S, Mehrabi A, Vogel MN, et al. Mismatch repair deficiency is a rare but putative therapeutically relevant finding in non-liver fluke associated cholangiocarcinoma. Br J Cancer. 2019;120(1):109–114.

Goyal L, Saha SK, Liu LY, Siravegna G, Leshchiner I, Ahronian LG, et al. Polyclonal secondary FGFR2 mutations drive acquired resistance to FGFR inhibition in patients with FGFR2 fusion-positive cholangiocarcinoma. Cancer Discov. 2017;7(3):252–263.

Graham RP, Barr Fritcher EG, Pestova E, Schulz J, Sitailo LA, Vasmatzis G, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol. 2014;45(8):1630–1638.

Helsten T, Elkin S, Arthur E, Tomson BN, Carter J, Kurzrock R. The FGFR landscape in cancer: analysis of 4,853 tumors by next-generation sequencing. Clin Cancer Res. 2016;22(1):259–267.

Jain A, Kwong LN, Javle M. Genomic profiling of biliary tract cancers and implications for clinical practice. Curr Treat Options Oncol. 2016;17(11):58. doi:10.1007/s11864-016-0432-2.

Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut. 2012;61:1657–1669.

Kheder ES, Hong DS. Emerging targeted therapy for tumors with *NTRK* fusion proteins. Clin Cancer Res. 2018;24(23):5807–5814.

Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol. 2014;25(12):2328–2338.

Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. ABC-06. A randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. Paper presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract #4003.

Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. J Hepatol. 2020;73(1):170–185.

Marabelle A, Le DT, Ascierto PA, Di Giacomo AM. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020;38(1):1-10.

Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015;9(47):1003–1110.

NCCN Clinical Practice Guidelines in Oncology – Hepatobiliary Cancers. Version 1.2020 – March 23, 2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

NCCN Clinical Practice Guidelines in Oncology – Hepatobiliary Cancers. Version 3.2020 –June 1, 2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

NCCN Clinical Practice Guidelines in Oncology – Hepatobiliary Cancers. Version 5.2020 – August 4, 2020. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

Parker BC, Engels M, Annala M, Zhang W. Emergence of FGFR family gene fusions as therapeutic targets in a wide spectrum of solid tumours. J Pathol. 2014;232(1):4–15.

Ross JS, Wang K, Gay L, Al-Rohil R, Rand JV, Jones DM, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19(3):235–242.

Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma incidence in the U.S.: intrahepatic disease on the rise. Oncologist. 2016;21:1–6.

Sia D, Losic B, Moeini A, Cabellos L, Hao K, Revill K, et al. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. Nat Commun. 2015;6:6087. doi:10.1038/ncomms7087.

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Sun W, Patel A, Normolle D, Patel K. A phase 2 trial of regorafenib as a single agent in patients with chemotherapy-refractory, advanced, and metastatic biliary tract adenocarcinoma. *Cancer*. 2019;125(6):902-909. doi:10.1002/cncr.31872

Touat M, Ileana E, Postel-Vinay S, Andre F, Soria J-C. Targeting FGFR signaling in cancer. *Clin Cancer Res*. 2015;21(12):2684–2694.

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273–1281.

Welzel TM, Graubard BI, El-Serag HB, Shaib YH, Hsing AW, Davila JA, et al. Risk factors for intra-hepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol*. 2007;5(10):1221–1228.

Wu YM, Su F, Kalyana-Sundaram S, Khazanov N, Ateeq B, Cao X, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov*. 2013;3(6):636–647.

FDA's Additional References:

De Oliveira M, Cunningham S, Cameron J, Kamangar F, Winetr J. et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007 May;245(5):755-62.

Rizvi S. and Gores G. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* . 2013 Dec;145(6):1215-29.

Krook M, Lenyo A, Wilberding M, Barker H, Dantuono M. Efficacy of FGFR Inhibitors and Combination Therapies for Acquired Resistance in FGFR2-Fusion Cholangiocarcinoma. *Mol Cancer Ther* 2020 Mar;19(3):847-857.

Kheder D and Hong D. Emerging targeted therapy for tumors with *NTRK* fusion proteins. *Clinical Cancer Research* 2019; 24(23): 5807-5814.

Peppers MP, Geheb M, Desai T. Hypophosphatemia and Hyperphosphatemia. *Critical Care Clinics* 1991; 7(1):201-14.

Gadab M, Saada A, FaisaluddincM, Mihnea A, Gaman N, Ruhban I et al. Epidemiology of Cholangiocarcinoma; United States Incidence and Mortality Trends. *Clinics and Research in Hepatology and Gastroenterology* Volume 44, Issue 6, November 2020, Pages 885-893

American Cancer Society (www.cancer.org)

Fostea RM, Fontana E, Torga G, Arkenau HT. Recent Progress in the Systemic Treatment of Advanced/Metastatic Cholangiocarcinoma. Cancers (Basel). 2020 Sep 11;12(9):2599.

Jain A, Kwong LN, Javle M. Genomic Profiling of Biliary Tract Cancers and Implications for Clinical Practice. Curr Treat Options Oncol. 2016 Nov;17(11):58.

Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010 Apr 8;362(14):1273-81.

Angela Lamarca, Daniel H. Palmer, Harpreet Singh Wasan, Paul J. Ross, Yuk Ting Ma, Arvind Arora, Stephen Falk, Roopinder Gillmore, Jonathan Wadsley, Kinnari Patel, Alan Anthoney, Anthony Maraveyas, Justin S. Waters, Claire Hobbs, Safia Barber, David Ryder, John Ramage, Linda M Davies, John A. Bridgewater, Juan W. Valle J Clin Oncol 37, 2019 (suppl; abstr 4003).

Lowery MA, Goff LW, Keenan BP, Jordan E, Wang R, Bocobo AG, Chou JF, O'Reilly EM, Harding JJ, Kemeny N, Capanu M, Griffin AC, McGuire J, Venook AP, Abou-Alfa GK, Kelley RK. Second-line chemotherapy in advanced biliary cancers: A retrospective, multicenter analysis of outcomes. Cancer. 2019 Dec 15;125(24):4426-4434.

19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure for all clinical investigators involved in Study CBGJ398X2204. Signed financial disclosure forms could not be obtained for 11 sub-investigators. Due diligence was conducted to attempt to obtain financial disclosures forms from the 11 sub-investigators. There were no principal investigators with disclosable financial arrangements.

The FDA's Assessment:

FDA agrees with the Applicant's position. See also "Financial Disclosure" in Section 8.1.2, above.

Covered Clinical Study (Name and/or Number):* CBGJ398X2204

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
--	--	---

Total number of investigators identified: <u>458</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

All relevant nonclinical pharmacology and toxicology assessments are provided in Section 5.

The FDA's Assessment:

N/A.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Concentrations of infigratinib and its metabolites (BQR917, CQM157, and BHS697) in human plasma were measured using bioanalytical methods based on liquid chromatography tandem mass spectrometry (LC-MS/MS). These methods were modified and improved over time and were also transferred between four bioanalytical laboratories: (1) Novartis, Basel, Switzerland; (2) (b) (4); (3) (b) (4); and finally (4) (b) (4). Table 54 below lists the bioanalytical method applied in the clinical studies.

Table 54. Summary of bioanalytical method performance in infigratinib clinical studies.

Clinical Study Number	Bioanalytical Laboratory	Bioanalytical Study Report	Bioanalytical Method Validation	Analyte	Biological Matrix	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
CBGJ398X1101	(b) (4)	DMPK RCBGJ398X1101	DMPK R1200785 & DMPK R1701243	Infigratinib BHS697 BQR917 CQM157	Plasma Plasma Plasma Plasma	1 1 1 1	-3.1 to 3.3 -2.4 to 3.0 -5.2 to 4.7 -7.6 to 5.0	3.4 to 18.2 3.7 to 8.2 5.0 to 22.6 2.9 to 19.8
CBGJ398X2101	Novartis	DMPK RCBGJ398X2101	DMPK R0800428b & DMPK R1400549	Infigratinib (up to run 112) BHS697 (up to run 112) BQR917 (up to run 113) Infigratinib (since run 114) BHS697 (since run 114) BQR917 (since run 114) CQM157 (since run 114)	Plasma Plasma Plasma Plasma Plasma Plasma Plasma Plasma	1 1 1 1 1 1 1 1	-0.9 to 1.7 0.0 to 1.3 -1.8 to 0.7 -3.0 to 1.0 -4.3 to -0.4 -0.5 to 4.0 -4.0 to -1.3	4.8 to 8.6 6.2 to 12.4 5.0 to 18.1 5.0 to 5.9 5.2 to 9.9 5.8 to 8.3 4.3 to 6.7
CBGJ398X2101b	(b) (4)	DMPK RCBGJ398X2101b	DMPK R1200785 & DMPK R1700986	Infigratinib BHS697 BQR917 CQM157	Plasma Plasma Plasma Plasma	1 1 1 1	-5.2 to 6.7 -5.9 to 5.0 -4.5 to -0.3 -4.7 to 5.3	3.2 to 6.3 4.8 to 8.2 3.0 to 5.6 2.4 to 6.6
CBGJ398X2102	(b) (4)	DMPK RCBGJ398X2102	DMPK R1200785 & DMPK R1700986	Infigratinib BHS697 BQR917 CQM157	Plasma Plasma Plasma Plasma	1 1 1 1	-0.5 to 0.7 0.3 to 1.7 -1.1 to 0.3 -4.3 to 0.3	3.9 to 6.1 5.2 to 7.3 4.7 to 9.1 4.1 to 7.0

NDA 214622 Multi-disciplinary Review and Evaluation
 Infigratinib (Truseltiq)

Clinical Study Number	Bioanalytical Laboratory	Bioanalytical Study Report	Bioanalytical Method Validation	Analyte	Biological Matrix	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
CBGJ398X2103	(b) (4)	DMPK RCBGJ398X2103	DMPK R1200785	Infigratinib	Plasma	1	-2.1 to 2.0	3.7 to 7.9
				BHS697	Plasma	1	-2.8 to 2.0	4.2 to 8.6
				CQM157	Plasma	1	-4.9 to 3.7	3.3 to 5.1
CBGJ398A2104		DMPK RCBGJ398A2104	DMPK R1200785	Infigratinib	Plasma	1	-1.7 to 0.3	2.9 to 5.4
				BHS697	Plasma	1	-1.9 to 0.3	4.0 to 7.3
				CQM157	Plasma	1	1.7 to 8.0	2.3 to 4.0
CBGJ398X2105		DMPK RCBGJ398X2105	DMPK R1200785	Infigratinib	Plasma	1	2.3 to 3.3	4.1 to 5.0
				BHS697	Plasma	1	1.3 to 3.0	4.9 to 6.7
				CQM157	Plasma	1	-1.3 to 4.3	3.1 to 6.1
CBGJ398X2106		DMPK RCBGJ398X2106	DMPK R1200785	Infigratinib	Plasma	1	-2.4 to 0.7	2.7 to 4.1
				BHS697	Plasma	1	-2.1 to 0.8	4.1 to 5.4
				CQM157	Plasma	1	-2.0 to 2.3	2.2 to 4.0
CBGJ398X2201		DMPK RCBGJ398X2201	DMPK R1200785 & DMPK R1701243	Infigratinib	Plasma	1	-0.7 to 1.3	2.8 to 4.3
				BHS697	Plasma	1	-0.8 to 2.7	5.0 to 9.5
				BQR917	Plasma	1	0.3 to 3.3	3.5 to 5.4
				CQM157	Plasma	1	-0.8 to 2.0	3.8 to 4.5
CBGJ398X2204		DMPK RCBGJ398X2204	DMPK R1200785	Infigratinib	Plasma	1	-1.3 to 0.1	3.6 to 4.0
				BHS697	Plasma	1	-1.0 to 3.3	4.4 to 6.2
				CQM157	Plasma	1	-2.0 to 2.3	3.1 to 5.5
CBGJ398X2204		DMPK RCBGJ398X2204 RPT04881	DMPK R1200785 & DMPK R1701243	Infigratinib	Plasma	1	-1.15 to -0.72	3.18 to 6.42
				BHS697	Plasma	1	-0.89 to 2.17	4.17 to 5.85
				CQM157	Plasma	1	-1.75 to 0.61	4.21 to 5.86
QBGJ398-101		DCN 4007390	DCN 4007614	Infigratinib	Plasma	0.2	to 5.0	4.2 to 5.7
				BHS697	Plasma	0.2	-3.8 to 3.0	2.8 to 5.3
				BQR917	Plasma	0.2	-2.0 to 6.0	3.6 to 7.6
				CQM157	Plasma	0.2	6.9 to 12.3	2.6 to 5.0
QBGJ398-102		DCN 4007723	DCN 4007614	Infigratinib	Plasma	0.2	-1.3 to 5.3	3.7 to 5.8
				BHS697	Plasma	0.2	-3.8 to -1.0	3.1 to 7.0
				BQR917	Plasma	0.2	-1.2 to 3.3	4.1 to 5.8
				CQM157	Plasma	0.2	6.2 to 10.5	3.1 to 8.1
QBGJ398-103		DCN 4007396	DCN 4007614	Infigratinib	Plasma	0.2	-1.9 to 10.0	2.7 to 4.8
				BHS697	Plasma	0.2	-3.1 to 1.0	2.3 to 6.8
				BQR917	Plasma	0.2	-0.6 to 3.8	2.9 to 5.6
				CQM157	Plasma	0.2	3.8 to 12.0	3.2 to 4.9
QBGJ398-104		DCN 4007612	DCN 4007614	Infigratinib	Plasma	0.2	1.3 to 8.5	4.3 to 6.4
				BHS697	Plasma	0.2	-2.5 to -0.5	3.5 to 5.1
				BQR917	Plasma	0.2	0.2 to 12.0	3.4 to 6.2
				CQM157	Plasma	0.2	6.3 to 15.0	3.2 to 6.1
QBGJ398-106		DCN 4007746	DCN 4007614	Infigratinib	Plasma	0.2	2.5 to 6.0	1.5 to 5.2
				BHS697	Plasma	0.2	-9.3 to -3.7	3.2 to 8.7
				BQR917	Plasma	0.2	-1.0 to 5.0	2.4 to 4.2
				CQM157	Plasma	0.2	-3.8 to 1.0	2.4 to 9.3
QBGJ398-106		DCN 4007746	DCN 4007746	Midazolam	Plasma	0.2	-2.2 to 1.3	2.5 to 3.8
				1-hydroxymidazolam	Plasma	0.2	-1.6 to 0.4	2.1 to 4.1
QBGJ398-107		DCN 4007398	DCN 4007398	Infigratinib	Plasma	0.2	-1.3 to 2.5	2.8 to 6.5
				BHS697	Plasma	0.2	-1.3 to 8.5	2.5 to 7.6
				BQR917	Plasma	0.2	-6.0 to -0.6	2.0 to 7.7
				CQM157	Plasma	0.2	-2.2 to 3.5	1.6 to 14.6
QBGJ398-107		DCN 4007398	DCN 4007398 (protein binding)	Infigratinib	Plasma	.045	-2.7 to 10.8	3.2 to 8.8
				BHS697	Plasma	.045	0.0 to 5.0	3.5 to 9.2
				BQR917	Plasma	.045	0.4 to 3.3	3.5 to 7.3
				CQM157	Plasma	.045	3.6 to 13.3	3.5 to 12.8
QBGJ398-109		DCN 4007394	DCN 4007614	Infigratinib	Plasma	0.2	-9.9 to 3.5	2.5 to 5.2
				BHS697	Plasma	0.2	-8.7 to -2.5	3.4 to 7.1
				BQR917	Plasma	0.2	-10.7 to 0.6	2.9 to 8.9
				CQM157	Plasma	0.2	-2.5 to 6.0	5.0 to 6.1

Source: EDR 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods
 Table 14.

19.4.2. Formulation Bridging

During the clinical development of infigratinib, various formulations (CSF, FMI I, FMI III, and FMI IV) were developed and administered to healthy volunteers and oncology patients. In Study CBGJ398X2204, formulations FMI-I, FMI-III, and FMI-IV were administered to patients with cholangiocarcinoma. The bridging of the to-be-marketed formulation FMI-IV to FMI-I and FMI-III was established based on the following:

1. FMI-IV to FMI-III:

According to Pharmaceutical Quality review, FMI-III and FMI-IV are deemed sufficiently similar in terms of formulation and manufacturing process. Adequate comparative in vitro dissolution data using the proposed dissolution method and in various pH media were also established. Therefore, the in vitro bridging is considered an appropriate approach to establish the bridging of FMI-IV to FMI-III. Refer to Pharmaceutical Quality review for details.

In a PK analysis with pooled PK data from 5 single dose healthy volunteer studies (i.e., Study CBGJ398X2103 [CSF, FMI-I], CBGJ398A2104 [CSF], CBGJ398A2105 [CSF], CBGJ398A2106 [CSF, FMI-III], QBGJ398-109 [FMI-IV]), the arithmetic mean value of dose-normalized infigratinib AUC_{inf} in Table 55 and overall $AUC_{activity}$ (defined in Section 6.2.2.1) in Table 56, are comparable with differences less than 20% across studies for FMI-III versus FMI-IV. Of note, using $AUC_{activity}$ for formulation comparison is based on consideration of: (1) the Applicant finding that orally administered infigratinib undergoes extensive first-pass hepatic extraction or presystemic metabolism prior to reaching general systemic circulation; and (2) the exposure-response assessment for safety does not show new safety signal with regard to the two active metabolites BHS697 and CQM157.

In addition, the population PK modeling assessment has demonstrated that the formulations have minimal effect on the PK of infigratinib or its metabolites. (Section 19.4.2)

It is noted that the C_{max} of infigratinib is higher in FMI-IV from Study 109 as compared to FMI-III from Study 2106 (Table 55). However, this difference is not considered as clinically relevant, based on the following:

- (1) The C_{max} relationship in patients following multiple doses may differ from that following a single dose and in healthy subjects. In addition, the comparison of C_{max} here is a cross study comparison.
- (2) Based on population PK modeling assessment, simulated PK parameters were available for formulations FMI-I, FMI-III, and FMI-IV in Study CBGJ398X2204 in patients following first dose and at steady state for infigratinib. (Table 57). The simulated infigratinib C_{max} and AUC_{0-24} , as well as overall $AUC_{activity}$ following the first dose and at steady state were

compared for FMI-III versus FMI-IV, and the differences in the geometric mean values of these metrics were all less than 20%.

- (3) In the exposure-response analysis, the Applicant evaluated all exposure metrics (e.g., C_{trough} , C_{max} , C_{avg} , AUC_{0-24} , etc.). Among these metrics, the overall $AUC_{activity}$ was found to have slightly better correlation with hyperphosphatemia and eye disorder than other metrics including infigratinib C_{max} . Given the simulated difference for probability of hyperphosphatemia and eye disorder between infigratinib dosage of 100 mg and 125 mg is small (Section 19.4.4), the < 20% difference of $AUC_{activity}$ (or C_{max}) for FMI-IV versus FMI-III is not likely to result in a clinically meaningful difference of the safety profile.

Given the adequacy of in vitro bridging establishment, lack of a statistically significant impact on PK by population PK analysis, as well as the in vivo AUC similarity across these two studies, the overall formulation bridging is still considered established. This conclusion is reached based on the overall consideration of the totality of safety, efficacy, PK, in vitro dissolution, and product quality comparability data.

Based on the above rationale, FMI-IV and FMI-III are considered adequately bridged.

2. FMI-I to FMI-III:

The majority of patients in Study CBGJ398X2204 received FMI-I (N=51) or FMI-III (N=48), as compared to FMI-IV (N=9). The pooled PK analysis across studies in Table 55 has demonstrated that the C_{max} , and T_{max} of infigratinib were similar for FMI-I and FMI-III. The infigratinib AUC_{inf} and the overall $AUC_{activity}$ (Table 56) also showed a difference of the mean values less than 20% for these two formulations.

In addition, the efficacy and safety of FMI-I and FMI-III did not appear to have clinically relevant difference in Study CBGJ398X2204.

Based on the above, FMI-III and FMI-I are considered adequately bridged.

3. FMI-IV to FMI-I:

Both FMI-IV and FMI-I have been bridged to FMI-III as demonstrated above. Similarly, the pooled PK analysis across studies has demonstrated that the infigratinib AUC_{inf} and the overall $AUC_{activity}$ of FMI-I and FMI-IV are comparable with a difference of mean values less than 20%. In vitro dissolution testing has also demonstrated the similarity between the two formulations.

It is also noted that the C_{max} of FMI-IV is higher than FMI-I in Table 55. However, this difference is not considered clinically relevant given the similar rationale as above for the higher C_{max} of FMI-IV as compared to FMI-III.

Given the lack of PK difference by formulation based on population PK, as well as the

establishment of bridging from FMI-IV and FMI-I to FMI-III, the overall formulation bridging is still considered established based on the totality of safety, efficacy, PK, and in vitro dissolution comparability data.

Based on the above, FMI-IV and FMI-I are considered adequately bridged.

Based on the above assessments, the bridging of FMI-IV to FMI-I and FMI-III is considered adequately established.

Table 55. Summary of dose normalized descriptive PK by formulations, based on 5 healthy volunteer studies CBGJ398X2103, CBGJ398A2104, CBGJ398A2105, CBGJ398A2106, QBGJ398-109.

PK Parameter	Formulation	Mean (%CV)					
		n	Infigratinib (BGJ398)	n	BHS697	n	CQM157
AUC _{inf} (h*ng/ mL/mg)	CSF	81	5.87 (157.10)	13	2.76 (70.15)	84	11.58 (60.00)
	FMI I	57	6.52 (133.34)	37	1.62 (102.04)	60	13.13 (57.98)
	FMI III	31	5.74 (112.69)	8	2.48 (45.47)	33	11.12 (73.42)
	FMI IV	20	5.95 (152.62)	20	2.17 (152.65)	20	9.45 (70.81)
C _{max} (ng/mL/mg)	CSF	89	0.44 (80.15)	84	0.06 (59.51)	89	0.36 (59.37)
	FMI I	62	0.43 (82.76)	59	0.06 (64.17)	62	0.43 (62.13)
	FMI III	35	0.41 (73.27)	34	0.06 (65.32)	35	0.34 (69.70)
	FMI IV	20	0.55 (75.03)	20	0.08 (57.50)	20	0.31 (56.43)
T _{max} ^a (h)	CSF	89	4.00 (2.00, 10.00)	84	3.00 (2.00, 12.00)	89	10.00 (3.00, 36.00)
	FMI I	62	4.00 (2.00, 36.00)	59	4.00 (2.00, 36.00)	62	10.00 (4.00, 24.00)
	FMI III	35	4.00 (2.00, 10.00)	34	4.00 (2.00, 6.00)	35	10.00 (4.00, 10.07)
	FMI IV	20	4.00 (1.99, 6.00)	20	4.00 (1.99, 4.09)	20	4.07 (3.99, 24.03)

Source: EDR 5.3.3.1 qed-001 Table 2.

Table 56. Descriptive statistics of dose normalized AUC_{activity} (μM*h/mg) by formulations across healthy volunteer studies.

Formulation	N	AUC _{activity}		N	AUC _{activity} FGFR2	
		Mean	CV%		Mean	CV%
CSF	127	0.1634	60.68	127	0.0554	58.03
FMI I	23	0.1643	62.25	23	0.0556	55.11
FMI II	68	0.1401	57.45	68	0.0478	55.15
FMI III	35	0.1464	62.17	35	0.0496	64.78
FMI IV	20	0.1512	84.67	20	0.0473	76.93

Source: Response to FDA RFI-Biopharmaceutics -6 Jan 2021.

Table 57. Summary of simulated geometric mean (CV%) of infigratinib C_{max} and overall AUC_{activity} following oral administration of infigratinib 125 mg (FMI-I, FMI-III and FMI-IV) on C1D1 and C1D15.

PK parameters	First Dose			Steady State		
	FMI-I (N=19)	FMI-III (N=48)	FMI-IV (N=12)	FMI-I (N=19)	FMI-III (N=48)	FMI-IV (N=12)
Infigratinib C _{max} (ng/mL)	64.75 (51.4%)	63.91 (108%)	76.04 (57.9%)	179.3 (26.1%)	177.2 (27.9%)	206.2 (19.8%)
Infigratinib AUC ₀₋₂₄ (ng*h/mL)	751.7 (54.1%)	735.6 (108%)	840.3 (77.4%)	3597 (27.6%)	3501 (27.2%)	3989 (16.1%)
Overall AUC _{activity} (μM*h)	15.54 (42.7%)	15.63 (58.4%)	13.75 (40.5%)	37.05 (29.3%)	36.70 (31.0%)	41.39 (19.3%)

Source: EDR 5.3.3.5 QED-PMX-001.

19.4.3. Population PK Analysis

19.4.2.1 Review Summary

The applicant's population PK analysis is acceptable for characterization of PK of infigratinib and its two active metabolites BHS697 and CQM157, exploration of the exposure-response relationships for efficacy and safety, dose adjustment for intrinsic and extrinsic factors, and designation for future investigation trials.

Intrinsic (tumor type, healthy, hepatic function, sex) and extrinsic (fed, dose, time, formulation) factors were identified as covariates on F_{rel} , KA , CL_{app} , V_{capp} , and V_{papp} in PK models of infigratinib or its active metabolites. Renal excretion is a minor route for infigratinib elimination, but creatinine clearance ($CrCL$) was identified as a covariate for CL_{app} . Amongst the identified covariates, most were not found to have a profound impact on overall activity AUC - a combined AUC of the parent drug and two active metabolites based on their relative *in vivo* EC50 potency of receptor binding for FGFR1-4. The estimated PK parameters, η and ϵ , and their shrinkages were reasonable (generally <30%) for EBE estimation used in PK/PD analyses.

The developed model was used to for simulation of different dose scenarios for organ impaired patients to match the exposure of patients with normal organ function. Though we agree with the Applicant's simulation results, dose adjustment proposed by the Applicant does not appear to be adequate. We recommend dose reductions for patients with mild or moderate hepatic or renal impairment (detailed in 19.4.2.4).

19.4.2.2 Population PK Assessment

19.4.2.2.1 Objectives

The primary objective of this assessment was to:

- To examine if the final population PK model reasonably describe the observations.
- To verify sponsor's exposure simulation and evaluate the adequacy of dose adjustment for patients with organ impairment based on PK matching with patients that have normal organ function.

19.4.2.2.2 Overview of studies included in population PK analysis

Data were pooled from 11 Phase 1 studies in healthy subjects and 2 Phase 2 studies in patients with advanced solid tumors or advanced or metastatic cholangiocarcinoma (Table 58).

Two interim datasets that were collected at different cut-off time were used for modeling. Base structure model development and covariate evaluation used interim dataset 1 (May 2019 cut-off); final model refinement used interim dataset 2 (March 2020 cut-off).

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Table 58. Studies Included for Population PK Analysis.

Study Number/ Phase	Study Title	Participants Planned or Observed	Infigratinib Formulation/ Duration of Dosing	Planned Exclusions
CBGJ398X1101/ Phase 1	A phase I study of oral BGJ398 in Asian patients with advanced solid tumor having alterations of the FGF-R pathway	Planned Total: at least 33 Dose Escalation: at least 12 Chinese Safety Lead-in: at least 1 Dose Expansion: at least 20	CSF 28-day cycles continuous daily dosing Dose Escalation: proposed levels ranged from 50 to 200 mg QD or BID with 3 to 6 patients per level Chinese Safety Lead-in: equal or less than the maximum dose confirmed tolerable in Japanese patients with 3 to 6 new patients per level Dose Expansion: selected dose from Japanese Dose Escalation and Chinese Safety Lead-in; total of 20 Asian subjects (at least 10 Chinese) or, if dose selected is race dependent, a total of 6 Japanese and 10 Chinese subjects; this period can include additional subjects or may be previously studied subjects	None
CBGJ398X2101/ Phase 1	A phase I, open-label, multi-center, dose escalation study of oral BGJ398, a pan FGF-R kinase inhibitor, in adult patients with advanced solid malignancies	Observed Total: 208 Daily Dosing for 28-Day Cycles: Dose Escalation: n = 43 Dose Expansion: n = 49 Dose Expansion (3 weeks on/1 week off): n = 116	CSF and FMI I formulations/ 28-day cycles continuous daily dosing Dose Escalation: 5, 10, 20, 40, 60, 100, and 125 mg QD and 50 mg BID Dose Expansion: 125 mg QD (2 treatment arms) 28-day cycles daily dosing (3 weeks on/ 1 week off) Dose Expansion: 125 mg daily (2 additional treatment arms)	Excluding 5- and 10-mg dose groups (generally nonquantifiable)
CBGJ398X2102/ Phase 1b	A phase Ib, open-label study of oral BGJ398 in combination with oral BYL719 in adult patients with select advanced solid tumors	Observed 62 total Dose Escalation: n = 38 Dose Expansion: n = 24	CSF formulation/ 28-day cycles daily dosing (3 weeks on/1 week off) Dose Escalation: 20, 40, 75, 90, 100, and 125 mg Dose Expansion: 125 mg All infigratinib treatments were administered with 28 continuous daily doses of BYL719	None
Study Number/ Phase	Study Title	Participants	Formulation/ Duration of Dosing	Planned Exclusions
CBGJ398X2103/ Phase 1	A randomized, single-center, open-label, crossover study evaluating the food effect of prototype - FMI BGJ398 and the relative bioavailability of prototype - FMI and CSF formulations of BGJ398 in healthy subjects	Observed Total: 24	Single doses of 100 mg in each period for 4 periods 14-day washout between periods • Treatment A - CSF formulation under fasting conditions • Treatment B - FMI I formulation under fasting conditions • Treatment C - FMI I formulation with a low-fat, low-calorie meal • Treatment D - FMI I formulation with a high-fat, high-calorie meal	None
CBGJ398A2104/ Phase 1	A phase I, randomized, open label, single center, two-period crossover study to determine the relative bioavailability of two oral formulations of BGJ398, the final market image (FMI) capsule formulation in reference to the BGJ398 clinical service form (CSF) capsule formulation, in healthy subjects	Observed Total: 30 (n = 28 completed the study)	Single doses of 125 mg in each period for 2 periods under fasted conditions 14-day washout between periods • Treatment Sequence 1: 125 mg FMI II formulation, washout, 125 mg CSF formulation • Treatment Sequence 2: 125 mg CSF formulation, washout, 125 mg FMI II formulation	Excluding: PK data from the FMI II formulation
CBGJ398X2105/ Phase 1	A randomized, single-center, open-label, crossover study evaluating the effect of food and dose on the relative bioavailability of the final market image version 2 formulation of BGJ398 in reference to the BGJ398 clinical service form in healthy subjects	Observed Total: 40 (n = 37 completed the study)	Single doses of 125 mg CSF and 75, 125, and 200 mg FMI II over 4 periods 14-day washout between periods • Treatment A: 125 mg CSF formulation under fasting conditions • Treatment B: 75 mg FMI II formulation with a low-fat, low-calorie meal • Treatment C: 125 mg FMI II formulation with a low-fat, low-calorie meal • Treatment D: 200 mg FMI II formulation under fasting conditions	Excluding: PK data from the FMI II formulation

NDA 214622 Multi-disciplinary Review and Evaluation Infigratinib (Truseltiq)

Study Number/ Phase	Study Title	Participants	Formulation/ Duration of Dosing	Planned Exclusions
CBGJ398X2106/ Phase 1	A randomized, single-center, open-label, crossover study evaluating the relative bioavailability of the final market image version 3 (FMI III) formulation of BGJ398 in reference to the BGJ398 clinical service form (CSF) and the effect of food on the FMI III formulation in healthy subjects	Observed Total: 40	Single doses of 125 mg CSF, 75 and 125 mg FMI III over 4 periods 14-day washout between periods • Treatment A: 125 mg CSF formulation under fasting conditions • Treatment B: 75 mg FMI III formulation under fasting conditions • Treatment C: 125 mg FMI III formulation under fasting conditions • Treatment D: 125 mg FMI III formulation with a high-fat, high-calorie meal	None
QBGJ398-102 Phase 1	An open-label, fixed-sequence study to evaluate the effect of multiple oral doses of rifampin on the pharmacokinetics of a single oral dose of infigratinib (BGJ398) in healthy adult subjects	Planned: Total 20	Day 1: Single dose of 125 mg infigratinib FMI III Days 5-13: Single doses of 600 mg rifampin QD Day 14: Second single dose of infigratinib co-administered with the last dose of rifampin	Data that were collected on Day 5 or later
QBGJ398-103 Phase 1	An open-label, 2-period, fixed-sequence study to evaluate the effect of itraconazole on the pharmacokinetics of infigratinib (BGJ398) in healthy subjects	Planned: Total 20	Single doses of 75 mg infigratinib FMI III 4 single doses of 200 mg itraconazole 14-day washout between periods Period 1: Single dose of 75 mg infigratinib FMI III Period 2: 200 mg itraconazole 4 days QD 4 th dose of itraconazole will be co-administered with a single dose of 75 mg infigratinib	Excluding Period 2 data
QBGJ398-104 Phase 1	An open-label, 2-period, fixed-sequence study to evaluate the effect of lansoprazole on the pharmacokinetics of infigratinib (BGJ398) in healthy subjects	Planned: Total 20	Single doses of 125 mg infigratinib FMI III 7 single doses of 30 mg lansoprazole 14-day washout between periods Period 1: Single dose of 125 mg infigratinib FMI III Period 2: 30 mg lansoprazole 7 days QD 5 th dose of lansoprazole will be co-administered with a single dose of 125 mg infigratinib	Excluding Period 2 data
Study Number/ Phase	Study Title	Participants	Formulation/ Duration of Dosing	Planned Exclusions
QBGJ398-109 Phase 1	An open-label, one-period, single-dose trial to evaluate the pharmacokinetics of infigratinib (BGJ398 formulation FMI IV) in healthy subjects	Planned: Total 20	FMI IV Single dose of 125 mg infigratinib	None
CBGJ398X2201/ Phase 2	A phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable glioblastoma	Planned Total: 34 Non-Surgical Group: n = 22 Surgical Group: n = 11	FMI I 28-day cycles daily dosing (3 weeks on /1 week off) 125 mg QD Surgical Group: 125 mg QD prior to surgery 28-day cycles beginning within 2 weeks postoperative	None
CBGJ398X2204 ^{a,b} / Phase 2	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	May 2019 cutoff Total (in PK dataset): 55 March 2020 cutoff Total (in PK dataset): 79	FMI I, FMI III, or FMI IV 28-day cycles daily dosing (3 weeks on /1 week off) 125 mg QD	None

Abbreviations: BGJ398, infigratinib; BID, twice daily; BYL719, alpelisib; CSF, clinical service form; FGF-R/FGFR, fibroblast growth factor receptor; FMI, final market image; FMI I, final market image version 1; FMI II, final market image version 2; FMI III, final market image version 3; FMI IV, final market image version 4; n, number of subjects; PK, pharmacokinetic; QD, once daily.

^a Indicates ongoing clinical trial.

^b Interim Dataset 1 contained Study CBGJ398X2204 data from the May 2019 cutoff and Interim Dataset 2 contained the data from the March 2020 cutoff.

Source: <\\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf> (page 65-68)

19.4.2.2.3 Final Population PK model

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.3 using first-order conditional estimation with INTERACTION option (FOCE+I). Concentrations collected before the first dose were excluded from the PK analysis as well as post-dose observations that were below the limit of quantification (BLQ). About 20~35% of post dose BLQ records (percentage vary by the analyte) were excluded for

analysis, many of which were collected during the absorption phase. These samples were undetectable likely due to a low solubility of the drug (BCS Class II compound).

Baseline patient characteristics of the population PK dataset are summarized in Table 59. The number of samples from 572 subjects for the parent drug and metabolites used for population PK analysis is summarized in Table 60. There are small discrepancies in the number of samples between the PK report from sponsors and the PK data received.

The PK of infigratinib and its metabolites BHS697 and CQM157 were independently modeled because of rapid first-pass metabolism in the liver. The plasma concentrations of infigratinib as well as the metabolites were described by a two-compartment disposition model with first-order absorption. Time-dependent decrease in elimination was expressed as a function of dose counts in infigratinib and BHS697.

Covariates explored included age, body weight, sex, race, formulation, study, dose, study population (healthy volunteer and patients of various tumors), fed status, BMI, AST, ALT, TBIL, NCI liver function category, total protein, CrCL, cancer type (cholangiocarcinoma vs. other cancers), treatment (monotherapy vs. combination therapy). The concomitant medications explored were BLY719 (only in CBGJ398X2102), CYP3A4 inhibitors/inducers, gastric pH-modifying agents, and phosphate binders. Most of the covariates were not found to have a clinically significant impact on the overall activity AUC which is a combined AUC of the parent drug and two active metabolites based on their in vivo EC50 potency.

The final population PK parameters for infigratinib, BHS697, and CQM157 are presented in the Table 61, Table 62, and Table 63, respectively. The final PK models of these three analytes were all parameterized in terms of K_a , CL_{app} , $V2_{app}$, Q_{app} , and $V3_{app}$, $ALAG1$, and $F1_{rel}$.

For infigratinib, estimated fixed and random effect parameters were estimated with good precision (%RSE < 29%). For infigratinib, the magnitude of the interindividual variability was high for CL_{app} (78.7% CV), $V2_{app}$ (74.9% CV), k_a (120% CV), and $F1$ (76.9% CV). Residual variability was moderate.

For BHS697, estimated fixed and random effect parameters were estimated with good precision (%RSE < 29%) except the covariance between $V3_{app}$ and K_a (46.8%). The magnitude of the interindividual variability was moderate for $V3_{app}$ (32.9% CV), but high for CL_{app} (67.2% CV), $V2_{app}$ (120% CV), k_a (149% CV), and $F1$ (63.7% CV). Residual variability was moderate.

For CQM157, estimated fixed and random effect parameters were estimated with good precision (%RSE < 29%). The magnitude of the interindividual variability was high for CL_{app} (68.6% CV), $V2_{app}$ (65.4% CV), $V3_{app}$ (103% CV), k_a (54.8% CV), and $F1$ (55.5% CV). Residual variability was moderate.

The diagnostic plots and visual predictive check for the final PK models of the three analytes were stratified by profile type (healthy, single dose, and multiple doses in patients). The infigratinib PK model presented a left-shift concentration-time profile compared to the actual observations in healthy adults and patients (Figure 12), indicating a poor fit for the absorption phase. The drug underwent extensive first-pass metabolism and therefore large variability among different populations (healthy adults, patients with solid tumors, glioblastoma, or cholangiocarcinoma) was present. In addition, there are great number of BLQ observations during absorption phase that were excluded during PK modeling, leading to a large eta shrinkage for V_{2app} and a prediction bias for the absorption phase.

In VPC plots of multiple doses, both the infigratinib and BHS PK models overpredicted concentrations at the 10th percentile (Figure 12 and Figure 13). This is because all BLQ observations were added back to the dataset before calculating the percentiles of the observed observations. For handling BLQ, sponsor applied LLOQ/2 to replace BLQ which resulted in moderate differences in fixed effect parameters and comparable GOF plots; sponsor also tested M3 method which resulted in unsuccessful minimizations. The model fit for the data could be improved if the healthy and patient population were modeled separately, and a partial recovery of clearance after a dosing holiday was factored in the model (see 19.4.2.2.5). Overall, the model fit is acceptable for the heterogeneous study populations.

Table 59. Summary of Baseline Demographic Characteristics and Laboratory Values in the Dataset.

Characteristics	level	Statistics
N		573
Dose, n (%)	20 mg	13 (2.3)
	40 mg	11 (1.9)
	50 mg	9 (1.6)
	60 mg	3 (0.5)
	65 mg	1 (0.2)
	75 mg	35 (6.1)
	90 mg	5 (0.9)
	100 mg	42 (7.3)
	125 mg	448 (78.2)
	150 mg	6 (1)
NCI liver function group, n (%)	Normal	454 (79.2)
	Mild B1	90 (15.7)
	Mild B2	19 (3.3)
	Moderate C	10 (1.7)
Disease status, n (%)	Healthy	211 (36.8)
	Patient	362 (63.2)
Race, n (%)	Caucasian	405 (70.7)
	Black	88 (15.4)
	Asian	46 (8)
	Other	34 (5.9)

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

Characteristics	level	Statistics
Sex, n (%)	Male	344 (60)
	Female	229 (40)
Age (y), Mean (SD)	50.3 (15)	
Weight (kg), Mean (SD)	74.7 (16.6)	
ALT (U/L), Mean (SD)		26.7 (28.8)
BMI (kg/m ²), Mean (SD)		25.78 (4.69)
Total protein (g/L), Mean (SD)		70.62 (6.16)

Source: <\\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf> (page 83)

Table 60. Number of Samples for Population PK Analysis in Interim Dataset 2 (March 2020 Cutoff) Stratified by Analyte.

No. of samples for PPK analysis	Parent	BHS697	CQM157
Applicant report	8810	8182	8145
PPK dataset (poolpk11)	8808	8180	8145

Source: <\\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf> (page 78-80)

Table 61. Parameter Estimates and SE from Final Infigratinib Population PK Model.

	Final Parameter Estimate		Magnitude of Interindividual Variability	
Parameter	Population Mean	%RSE	Final Estimate	%RSE
k _a : First-Order Absorption Rate Constant (1/h)	0.228	11.1	123 %CV	6.66
k _a : Proportional Shift in k _a for FEDP = 1	0.832	23.8		
k _a : Proportional Shift in k _a for FEDH = 1	-0.416	3.59		
CL _{Bapp} : Base Apparent Central Clearance (L/h)	329	6.62	76.7 %CV	7.46
V _{2app} : Apparent Central Volume of Distribution (L)	1180	5.98	83.0 %CV	13.9
V _{2app} : Exponent of (DOSE/125) for V _{2app}	0.598	11.6		
Q _{app} : Apparent Intercompartmental Clearance (L/h)	59.7	5.37	NE	NA
V _{3app} : Apparent Peripheral Volume of Distribution (L)	796	5.04	NE	NA
ALAG1: Absorption Lag Time (h)	0.466	0.182	NE	NA
CL _{app} : Proportional Shift in CL _{app} for TUMSOLID = 1	-0.283	21.4	NE	NA
CL _{app} : Proportional Shift in CL _{app} for TUMGLCH = 1	-0.485	13.2		
KCLMAX: Maximal Relative Change of CL _{app}	-0.802	0.947	NE	NA
DC50: Dose Count of 50% Change of CL _{app}	1.67	7.61	NE	NA
F _{1rel} : Proportional Shift in F _{1rel} for FORM134 = 1	0.334	20.1	NE	NA
IOV in F _{1rel}	NA	NA	76.8 %CV	5.12
cov(IIV in V _{2app} , IIV in k _a) ^a	0.427	13.3	NA	NA
RV Additive	1.53	3.12	39.0 – 130 %CV ^b F [1 - 1400]	NA
RV Constant Coefficient of Variation	0.152	1.75		
Minimum Value of the Objective Function = 67023.081				

Source: <\\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf> (page 99)

Table 62. Parameter Estimates and SE from Final BHS697 Population PK Model.

	Final Parameter Estimate		Magnitude of IIV	
Parameter	Population Mean	%RSE	Final Estimate	%RSE
k _a : Absorption Rate Constant (1/h)	0.669	7.44	149 %CV	9.40
k _a : Proportional Shift in k _a for FORM1 = 1	-0.262	15.7		
k _a : Proportional Shift in k _a for FORM34 = 1	-0.0956	41.0		
CLB _{app} : Base Apparent Central Clearance (L/h)	821	5.47	67.2 %CV	7.14
V2 _{app} : Apparent Central Volume of Distribution (L)	8280	7.38	120 %CV	10.3
Q _{app} : Apparent Intercompartmental Clearance (L/h)	1620	4.55	NE	NA
V3 _{app} : Apparent Peripheral Volume of Distribution (L)	16100	7.09	32.9 %CV	24.4
V3 _{app} : Prop Shift in V3 _{app} for TUMSLGL = 1	-0.304	18.7		
V3 _{app} : Prop Shift in V3 _{app} for TUMCHOL = 1	-0.409	15.0		
V3 _{app} : Prop Shift in V3 _{app} for NCILIVBC = 1	-0.171	18.5		
ALAG1: Absorption Lag Time (h)	0.820	0.364	NE	NA
KCLMAX: Maximal Relative Change of CL _{app}	-0.704	1.16	NE	NA
DC50: Dose Count of 50% Change of CL _{app}	1.73	7.03	NE	NA
F1 _{rel} : Relative F1 in Patients	1.56	5.11	NE	NA
IOV in F1 _{rel}	NA	NA	63.7 %CV	3.93
cov(IIV in CLB _{app} , IIV in k _a) ^a	0.211	20.2	NA	NA
cov(IIV in V2 _{app} , IIV in k _a) ^b	0.724	11.3	NA	NA
cov(IIV in V2 _{app} , IIV in CLB _{app}) ^c	0.316	13.3	NA	NA
cov(IIV in V3 _{app} , IIV in k _a) ^d	0.0836	46.8	NA	NA
cov(IIV in V3 _{app} , IIV in CLB _{app}) ^e	0.135	19.8	NA	NA
cov(IIV in V3 _{app} , IIV in V2 _{app}) ^f	0.152	27.5	NA	NA
RV Additive	0.390	2.21	66.2 - 22.1 %CV ^g F [1.0 - 330]	NA
RV Constant Coefficient of Variation	0.0488	1.24		
Minimum Value of the Objective Function = 34389.341				

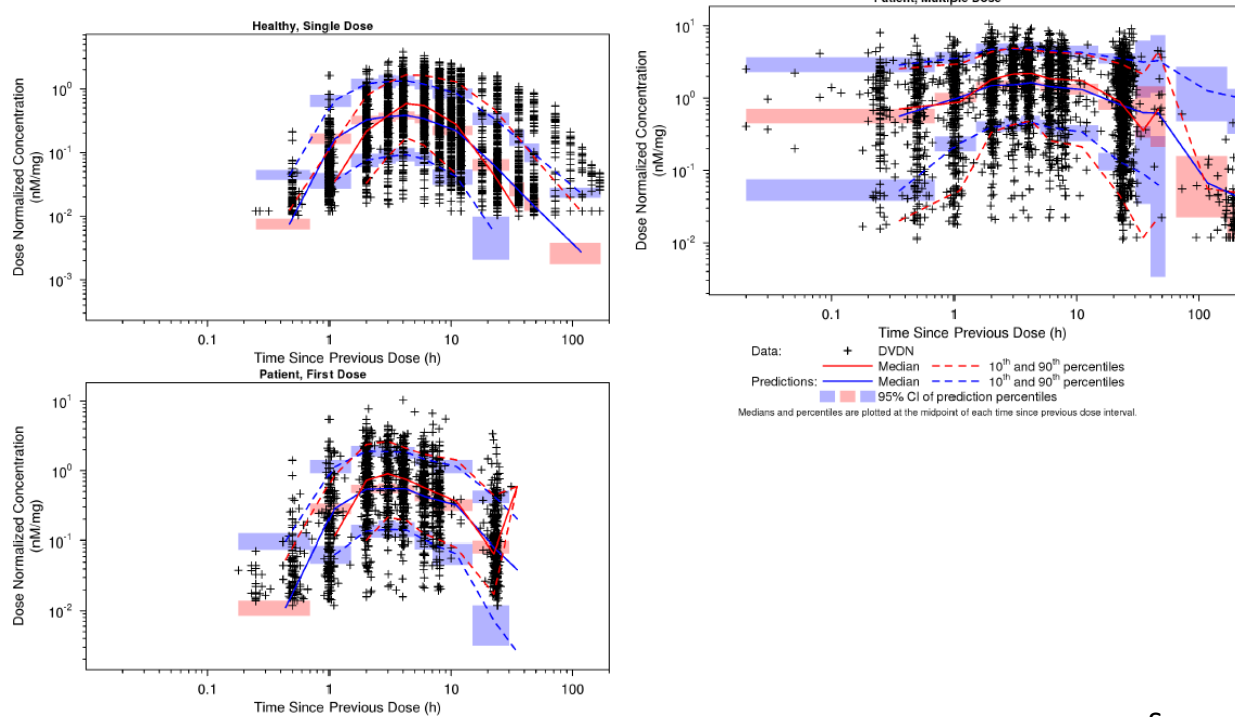
Source: \\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf (page 106)

Table 63. Parameter Estimates and SE from Final CQM157 Population PK Model.

Parameter	Final Parameter Estimate		Magnitude of Interindividual Variability	
	Population Mean	%RSE	Final Estimate	%RSE
k_a : Formation Rate Constant (1/h)	0.1005	6.869	81.31 %CV	12.89
k_a : Relative Change of k_a in Patients	0.5588	6.185		
CL_{app} : Apparent Clearance (L/h)	91.06	5.105	72.55 %CV	7.696
$V2_{app}$: Apparent Central Volume of Distribution (L)	883.9	7.634	99.20 %CV	9.856
$V2_{app}$: Exponent of (DOSE/100) for $V2_{app}$	0.5617	8.411		
Q_{app} : Apparent Intercompartmental Clearance (L/h)	48.83	4.164	NE	NA
$V3_{app}$: Apparent Peripheral Volume of Distribution (L)	1287	9.467	118.0 %CV	13.72
$V3_{app}$: Proportional Shift in $V3_{app}$ for FEDP = 1	1.844	12.12		
$V3_{app}$: Proportional Shift in $V3_{app}$ for FEDLH = 1	-0.1415	32.08		
ALAG1: Absorption Lag Time (h)	0.4707	0.4067	NE	NA
$F1_{rel}$: Relative Change of F1 for Multiple Dose in Patients	0.3533	2.362	NE	NA
$F1_{rel}$: Relative Change of F1 for BYL719	1.458	7.709		
$F1_{rel}$: Proportional Shift in F1 for SEXF = 1	0.6104	14.54		
IOV in $F1_{rel}$	NA	NA	48.35 %CV	5.657
cov(IIV in CL_{app} , IIV in k_a) ^a	-0.1218	30.07	NA	NA
cov(IIV in $V2_{app}$, IIV in k_a) ^b	0.2826	20.66	NA	NA
cov(IIV in $V2_{app}$, IIV in CL_{app}) ^c	0.2225	21.24	NA	NA
cov(IIV in $V3_{app}$, IIV in k_a) ^d	-0.3518	21.02	NA	NA
cov(IIV in $V3_{app}$, IIV in CL_{app}) ^e	0.5333	10.13	NA	NA
cov(IIV in $V3_{app}$, IIV in $V2_{app}$) ^f	0.1663	45.09	NA	NA
RV Additive	0.9570	6.943	101.8 - 28.02 %CV ^g	NA
RV Constant Coefficient of Variation	0.07851	1.490		
Minimum Value of the Objective Function = 48203.458				

Source: \\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf (page 116)

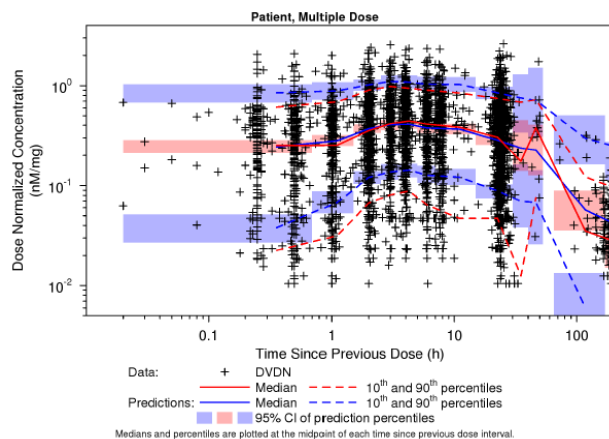
Figure 12. VPC for Infigratinib PPK Model in Double-log Scale, Stratified by Profile Type.



Source:

\\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf (page 217-218)

Figure 13. VPC for BHS697 PPK Model in Double-log Scale, Stratified by Profile Type.



Source: \\CDSESUB1\evsprod\NDA214622\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\qed-pmx-001\qed-pmx-001.pdf (page 256)

19.4.2.2.4 Elevated AUC in Organ Impaired Patients with Repeated Doses of Infigratinib

A significant accumulation of the parent drug (5-fold) and metabolite BHS697 (7-fold) was observed on day 15 compared to day 1 in terms of AUC₀₋₂₄. The effects of hepatic and renal impairment evaluated in dedicated study with a single dose of infigratinib may neither be adequate nor relevant. In addition, hepatic function was classified differently for healthy subjects in the dedicated study (Child-Pugh) and patients with cancer (NCI liver function group), therefore the degree of hepatic impairment could have discordance to directly apply dose recommendation based on one classification to the other.

The impact of hepatic or renal dysfunction in lieu of multiple doses was evaluated based on individual exposure estimation using population PK approach. In the pivotal study, hepatic impairment characterized by NCI liver function group included 36 patients in mild group (29 in B1 and 7 in B2), and 5 in moderate group; renal impairment characterized by creatinine clearance included 20 patients in mild group (60~89 mL/min) and 7 in moderate group (30~59 mL/min). As shown in Table 64, steady state AUC values for the parent and its active metabolites were increased in mild and moderate organ impaired subjects, except there is some inconsistency for CQM157.

Table 64. Ratio of AUC Geomean Relative to Normal Hepatic/renal Function for Each Organ Impairment Category in Study 2204.

Ratio of AUC Geomean Relative to Normal Hepatic/Renal Function	Hepatic impairment by NCI liver Fx group			Renal impairment by CrCL	
	Mild (B1)	Mild (B2)	Moderate (C)	Mild (60-89 mL/min)	Moderate (30-59 mL/min)
Infigratinib	1.65	1.86	2.19	1.39	1.48
BHS697	1.65	1.47	1.83	1.24	1.78
CQM157	0.86	1.29	2.00	1.25	0.69

Source: [\\CDSESUB1\evsprod\nda214622\0013\m1\us\111-info-amend\clin-info-amendment-clinpharm.pdf](#) (Derived from Table 12); [\\CDSESUB1\evsprod\nda214622\0009\m1\us\111-info-amend\clin-info-amend-clinpharm-14dec20.pdf](#) (Derived from Table 5)

Simulation to match PK for organ impaired patients

Since an elevation of exposure was observed in patients with hepatic/renal impairment, the Applicant performed PK simulations to determine the appropriate dose adjustment. To check if dose reduction is necessary, 5-95th percentile of simulated AUC activity of patients with normal organ function was used as the reference range and the organ impairment with 25-75th exposure outside of the reference range was considered for a dose reduction. Therefore, only patients with moderate hepatic impairment were proposed for a dose reduction to 75 mg (Table 65 and Table 66). Though most of the simulated AUC in mild hepatic impaired and mild/moderate renal impaired patients were within the reference range, the distribution displayed a prominent upward shift (Figure 14 and Figure 15). In addition, the simulation is based on a small number of

subjects, thus it is more appropriate to match the point estimate (geomean) and distribution, rather than using a wide reference range to determine the necessity of dose adjustment. Therefore, dose reduction to 100 mg is recommended for patients with mild hepatic impairment or mild-to-moderate renal impairment, and 75 mg is recommended for patients with moderate hepatic impairment.

Table 65. Geometric Mean of Simulated Exposures at 125, 100, and 75 mg by Hepatic Impairment Category in Study 2204.

NCI-ODWG	N	125 mg		100 mg		75 mg	
		AUC _{Activity} Geometric Mean and 90% CI		AUC _{Activity} Geometric Mean and 90% CI		AUC _{Activity} Geometric Mean and 90% CI	
Healthy	38	38.8	(22.57 - 67.34)	31.04	(18.06 - 53.87)	23.28	(13.54 - 40.41)
Mild B1	29	56.96	(34.43 - 114.98)	45.57	(27.54 - 91.98)	34.18	(20.66 - 68.99)
Mild B2	7	62.88	(42.07 - 82.62)	50.31	(33.66 - 66.1)	37.73	(25.24 - 49.57)
Moderate	5	77.4	(50.71 - 127.51)	61.92	(40.57 - 102.01)	46.44	(30.43 - 76.51)

Source: [\\CDSESUB1\evsprod\nda214622\0013\m1\us\111-info-amend\clin-info-amendment-clinpharm.pdf](#) (Page 13)

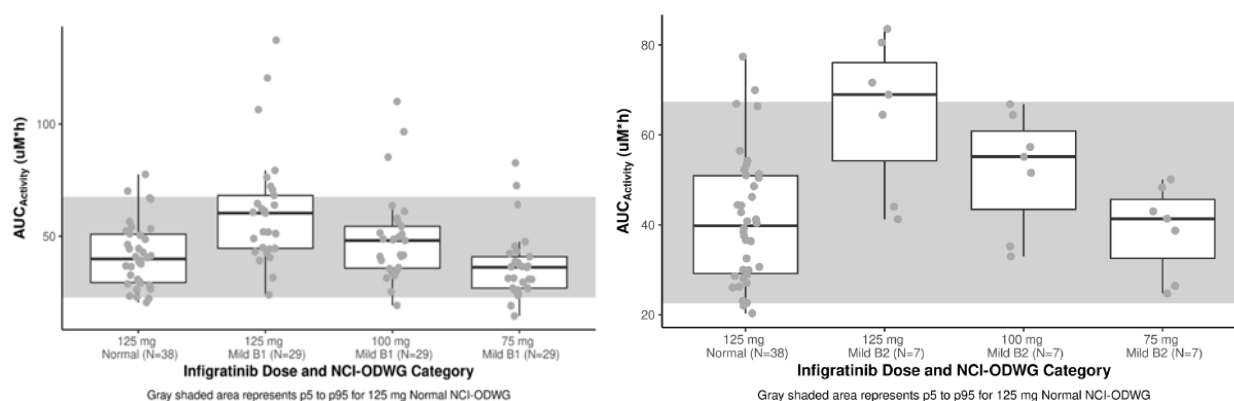
Table 66. Geometric Mean of Simulated Exposures at 125, 100, and 75 mg by Renal Impairment Category in Study 2204.

NCI	N	125 mg		100 mg		75 mg	
		AUC _{Activity} Geometric Mean and 90% CI		AUC _{Activity} Geometric Mean and 90% CI		AUC _{Activity} Geometric Mean and 90% CI	
Normal Function (CrCL $\geq$ 90 mL/min)	52	41.4	(22.25 - 70.64)	33.12	(17.8 - 56.51)	24.84	(13.35 - 42.38)
Mild Renal Impairment (CrCL [60, 90) mL/min)	20	54.7	(33.96 - 103.49)	43.76	(27.17 - 82.79)	32.82	(20.37 - 62.09)
Moderate Renal Impairment (CrCL [30, 60) mL/min)	7	56.92	(38.54 - 73.79)	45.54	(30.83 - 59.03)	34.15	(23.13 - 44.27)

Source: [\\CDSESUB1\evsprod\nda214622\0013\m1\us\111-info-amend\clin-info-amendment-clinpharm.pdf](#) (Page 15)

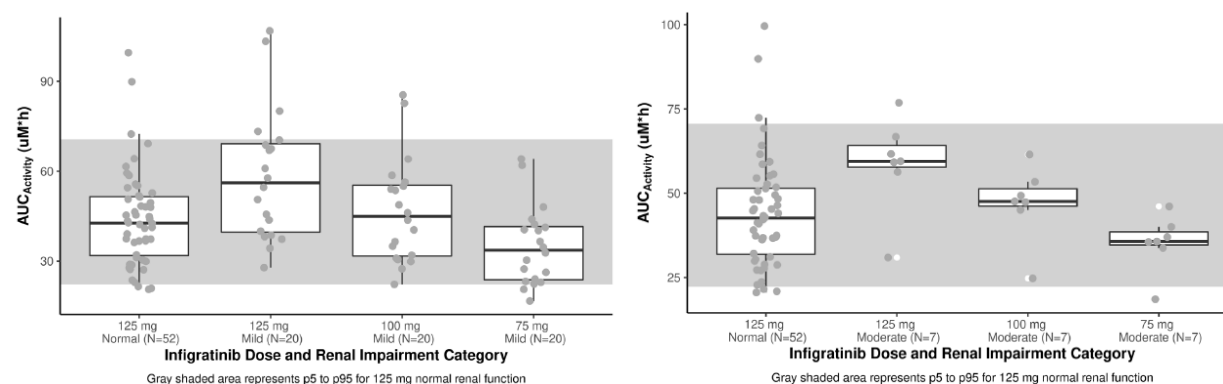
Note: One minor error in these tables provided by sponsor is noticed for the so called '90% CI'. These values appear to be 5-95th percentile of the simulated concentrations rather than the CI of geomean.

Figure 14. Overall activity AUC_{0-24h} in Mild (B1, B2) Hepatic Impairment by Simulated Doses of 125, 100, and 75 mg compared to Normal Hepatic Function.



Source: [\\CDSESUB1\evsprod\nda214622\0013\m1\us\111-info-amend\clin-info-amendment-clinpharm.pdf](#) (Page 14)

Figure 15. Overall activity AUC_{0-24h} in Renal Impairment by Simulated Doses of 125, 100, and 75 mg compared to Normal Renal Function.



Source: [\\CDSESUB1\evsprod\nda214622\0013\m1\us\111-info-amend\clin-info-amendment-clinpharm.pdf](#) (Page 16)

Reviewer's analysis

PK matching was performed by the Applicant in response to IR [20201218_FDA_NDA_RFI_ClinPharm_FINAL_AC], the method was not described in detail in the IR response. We verified the Applicant simulation through the following steps: 1) supplement hourly records up to 15 days after the first dose for Study 2204 data extracted from in poolpk11 dataset; 2) estimate individual PK parameters using the final infigratinib, BHS697, and CQM157 population PK models; 3) add dosing records for the days with dose interruption, and update dose count and dose that are used as covariates for time-dependent change on clearance and dose-dependent change on

volume, then generate 4 separate datasets for 50 mg, 75 mg, 100 mg, and 125 mg dose scenarios by replacing the existing dose amount in the dataset; 4) simulate hourly concentrations for the 4 dose scenarios; 5) summarize exposure (AUC_{0-24h} activity at steady state and C_{max} of infigratinib) based on baseline organ impairment categories.

The AUC activity profiles as shown in Table 67 and Figure 16 were similar to sponsor's profiles. Based on comparing the median and 90% CI of geomean, and weighing the distribution of simulated exposures, we recommend dose reductions for mild/moderate organ impaired subjects as follows:

- Hepatic impairment (by NCI classification): 25 mg dose reduction in patients with mild (B1 or B2) hepatic impairment; 50 mg dose reduction in patients with moderate (C) hepatic impairment.
- Renal impairment (by CrCL): 25 mg dose reduction in patients with mild (60-89 mL/min) or moderate (30-59 mL/min) renal impairment.

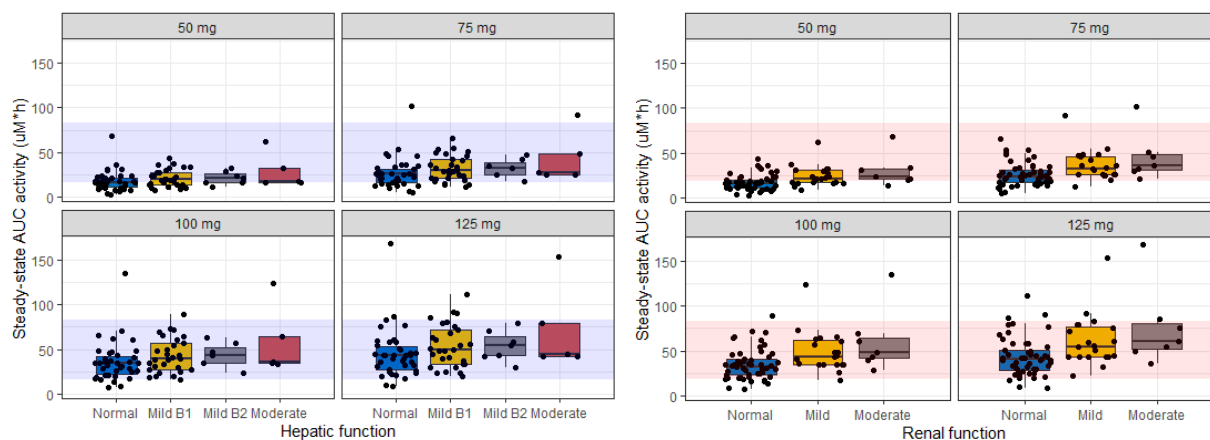
Table 67 Geometric Mean of Simulated AUC_{0-24h} Activity and Infigratinib C_{max} at 50, 75, 100, 125 mg by Organ Impairment Category in Study 2204.

AUC _{0-24h} activity (μM*h)				
Hepatic Impairment	Normal (A)	Mild (B1)	Mild (B2)	Moderate (C)
50 mg	15.6 [13.4; 18.2]	19.7 [17.1; 22.8]	20.7 [16.1; 26.6]	25.4 [14.8; 43.6]
75 mg	23.4 [20.1; 27.3]	29.5 [25.5; 34.1]	31 [24.2; 39.8]	38 [22.2; 65.1]
100 mg	31.1 [26.7; 36.3]	39.2 [33.8; 45.3]	41.4 [32.3; 53]	50.5 [29.4; 86.6]
125 mg	38.8 [33.3; 45.4]	48.8 [42.1; 56.5]	51.7 [40.5; 66]	62.9 [36.7; 108]
Renal Impairment	Normal (≥ 90 mL/min)	Mild (60-89 mL/min)	Moderate (30-59 mL/min)	
50 mg	15.6 [13.8; 17.5]	22.7 [19.4; 26.7]	27.1 [18.8; 39.1]	
75 mg	23.3 [20.7; 26.2]	34 [29; 40]	40.6 [28.2; 58.5]	
100 mg	31 [27.5; 34.8]	45.3 [38.5; 53.3]	54.1 [37.6; 77.8]	
125 mg	38.6 [34.3; 43.5]	56.5 [48; 66.5]	67.5 [47; 97]	

Infigratinib C _{max} (ng/mL)				
Hepatic Impairment	Normal (A)	Mild (B1)	Mild (B2)	Moderate (C)
50 mg	83.9 [69.7; 100.9]	114.3 [96.6; 135.3]	123.6 [96.4; 158.5]	123.9 [71.2; 215.7]
75 mg	117.9 [97.9; 142.1]	160.1 [135.1; 189.7]	174.5 [136.5; 223]	177.8 [100.7; 313.7]
100 mg	150.6 [124.8; 181.7]	204.1 [172; 242.2]	223.6 [175.4; 284.9]	229.9 [128.9; 410]
125 mg	182.3 [150.9; 220.3]	246.9 [207.7; 293.4]	271.6 [213.7; 345.1]	280.8 [156.1; 504.9]
Renal Impairment	Normal (≥ 90 mL/min)	Mild (60-89 mL/min)	Moderate (30-59 mL/min)	
50 mg	86 [74.5; 99.3]	130.8 [110.6; 154.8]	137.1 [83.5; 225.1]	
75 mg	120.5 [104.3; 139.3]	184.7 [156.2; 218.5]	196.3 [119.8; 321.7]	
100 mg	153.5 [132.6; 177.5]	236.9 [200.1; 280.5]	253.8 [155; 415.4]	
125 mg	185.4 [160.1; 214.7]	287.9 [242.8; 341.5]	310.1 [189.6; 507.1]	

Source: Reviewer's analysis

Figure 16. Simulated Overall Activity AUC_{0-24h} by Organ Impairment Categories at 50, 75, 100, and 125 mg.



Source: Reviewer's analysis

19.4.2.2.5 Technical issues with the sponsor's analyses

Inaccurate clearance and half-life estimates of infigratinib in cholangiocarcinoma patients proposed in the label

The steady state clearance of infigratinib was reported to be (b) (4) L/h ((b) (4) %CV) in proposed label and clin pharm summary. When referring to the source table [QEDT-NCA-BGJ398-827 Table 8.4.1.4], the clearance of infigratinib clearance at Cycle 1 Day 15 was reported as follows: the arithmetic mean - 25.35 L/h, geometric mean - 22.69 L/h, and median - 19.4 L/h, none of which matched (b) (4) L/h. In addition, the value of clearance is summarized from 7 subjects which may be biased due to small sample size.

The terminal half-life (*sponsor mistakenly named it as* (b) (4)) of infigratinib at steady state was reported to be (b) (4) hours in proposed label and clin pharm summary (b) (4)

Due to the limitations stated above in NCA analysis, below provided the clearance and half-life at Cycle 1 Day 15 calculation based on the population PK parameter estimates (the values of the parameter estimates can be found in population PK report):

- $CL_{ss} = CL_{app} * (1 - 0.489 * TUMGLCH) * [1 + KCLMAX * DC / (DC50 + DC)] = 47.2 \text{ L/h}$
 $F1_{rel} = 1 * (1 + 0.334 * FORM134) = 1.334$
 $CL_{app,ss} = CL / F1_{rel} = 35.4 \text{ L/h}$

Where $DC(\text{dose count})=15$ for steady-state; $TUMGLCH=1$ for cholangiocarcinoma patients; $KCLMAX$ (maximum relative change of clearance)=-0.802; $F1_{rel}$ stands for relative bioavailability to CSF formulation.

- $t_{1/2} = 0.693/BETA = 33.0$ h

BETA is the elimination constant for the terminal phase calculated as follows:

$$K23=Q_{app}/V2_{app}$$

$$K32=Q_{app}/V3_{app}$$

$$K=CL/V2_{app}$$

$$BETA = \{(K23 + K32 + K20) - \text{SQRT}[(K23 + K32 + K20)^2 - (4*K21*K20)]\}/2$$

The calculated values were in agreement with the PK estimates submitted by sponsor [20210209_FDA_NDA_RFI_ClinPharm].

Clearance of infigratinib partially restored after off-cycle

A reduction in infigratinib clearance (the parent drug and metabolite BHS697) over time was reflected with dose count as a covariate on clearance in the population PK model. Within a treatment cycle, trough increases with the number of dosing. At the start of a new cycle, a trough comparable to the level of the first dose in cycle 1 was observed, suggesting a restoration of clearance after the 7-day off-cycle. There is no inter-occasional variability was used to factor in this change, therefore the exposure measure could be inflated which likely introduced bias in the subsequent E-R analysis. Reviewer carried out an independent analysis to reset the dose count to 1 after the off-cycle (a reset for any dose holiday that lasted for at least 7 days). The OFV was increased, suggesting a complete restoration is not likely. Subsequently, the reviewer carried out another analysis by subtracting the number of dose holidays from the dose count. OFV of the infigratinib model dropped by 31.492, and OFV of the BHS697 model dropped by 8.928, suggesting some recovery from auto-inhibition after dose holidays. However, given the limited sparse PK sampling at the later cycles, the effect of off-cycle on clearance may not be adequately characterized and its impact on ER analyses and PK simulation for dose adjustment is expected to be minimum.

Large inter-occasional variability for Ka in BHS697 PK model

Large inter-occasional variability (IOV) for Ka was observed, accompanied by flip-flop kinetics in some subjects. Adding occasion to factor in IOV on Ka significantly improved the fit, partially resolving the flip-flop kinetics. Given BHS697 is a metabolite and the Ka is not a true absorption constant, the flip-flop in some subjects could be attributed by some transient extrinsic factors, such as concomitant medication. Since the change of key parameter estimates was within 20% and BHS697 only contributed to 16-33% of FGFR1-3 inhibition, the inter-occasional variability is expected to have minimal impact on exposure for subsequent ER analyses and PK simulation for dose adjustment.

Increased dose proportionality cross dose range not factored in population PK model

With NCA analysis for Study 2101, infigratinib exposures were found to increase more than dose proportionally across the dose range of 5 mg to 150 mg at steady state and accumulated significantly following repeated dosing. In population PK model however, only time-dependent effect was factored on clearance. This could result in an overestimation of exposure for a lower dose if dose proportionality is present.

Notably, there were few subjects per dose (1-4 for doses other than 125 mg) used in dose proportionality analysis in Study 2101 and large variability in exposures were observed between subjects and between days 15 and 28 with continuous dosing. In addition, C_{max} of infigratinib for low doses, 5 mg and 10 mg doses for instance, were around LLOQ, likely resulting in an underestimation of AUC. For dose of 60 mg-125 mg, AUC appear to be proportional to dose. Taken together, the dose proportionality is inconclusive based on the current assessment.

Minor errors

- Applicant used inconsistent unit for overall AUC activity throughout PK and ER report. The correct $AUC_{activity}$ unit should be $\mu M \cdot h$.
- In Table 16 of qed-pmx-001.pdf, CV of residual variability constant coefficient in interim model and interim model applied to interim dataset 2 was reversed.
- In qed-pmx-001.pdf, CrCL was indicated as a time-varying covariate. In the dataset for population PK however, only baseline CrCL was included in the population PK dataset.

Overall, given a substantial drug accumulation, the dedicated study in evaluation of intrinsic and extrinsic factors on exposure with single dose might not be very relevant. Therefore, population PK model was used to simulate steady state exposure for patients with organ impairment to justify dose adjustment. We agreed with sponsor's proposal of 50 mg dose reduction for patients with moderate hepatic impairment but concerned about overexposure in patients with mild hepatic and/or mild-to-moderate renal impairment. As detailed in 19.4.2.2.4, we recommend a 25 mg dose reduction for patients with mild hepatic impairment or mild-to-moderate renal impairment to match the distribution of exposure in patients with normal hepatic/renal function. In the IR response submitted on 1/11/2021 [20210111_FDA_NDA_RFI_Clin Pharm Response_AC], sponsor agreed dose reduction to 100 mg for mild hepatic impaired subjects.

Due to the paucity of the data for concomitant use of moderate CYP3A4 inducers/inhibitors, the exposure matching approach using modeling and simulation could not be conducted. We issued a PMR to evaluate the impact of drug-drug interactions in intent-to-treat population.

19.4.4. Exposure-Response Analysis

19.4.3.1 Review Summary

The Applicant's E-R analyses are acceptable for exploratory purposes to evaluate the impact of exposure on treatment response (BOR and PFS), and AE risk (hyperphosphatemia and eye disorder) in cholangiocarcinoma patients.

For treatment response, two efficacy endpoints (BOR, PFS) were modeled separately. The occurrence of OR was characterized by a logistic regression with various exposure measures (steady-state and average C_{max} , C_{trough} , AUC_{0-24h} of infigratinib/metabolites, overall activity AUC_{0-24h}) as covariates. Disease progression was characterized by Cox proportional hazard model with daily exposure measures. No E-R relationship was found for these two endpoints. There is no significant discordance identified, but such analyses given frequent dose interruption and reduction as well as treatment discontinuation, may lead to survival bias – a better response for a lower exposure.

For AE model, the drug-induced first occurrence of hyperphosphatemia/eye-disorder event was characterized by Cox proportional hazard model with daily exposure measures. In hyperphosphatemia model, data organization for time-dependent time-to-event analysis was found to be erroneous, resulting in the identification of phosphate binder as a positive covariate. In this model, the effect of infigratinib exposure was underestimated. the Applicant then used the model to predict the probability of hyperphosphatemia for 4 dose scenarios and concluded a small reduction in probability of hyperphosphatemia (3.3%, 7.8%, 14.5%) when dose was reduced to 100, 75, and 50mg. The magnitude of reduction was larger (4%, 9.4%, 17.1%) in reviewer's analysis after correcting the data organization issue.

19.4.3.2 Exposure-Response Assessment

19.4.3.2.1 Objectives

The primary objective of the assessment was to:

- To assess the relevance and adequacy of the exposure-response analyses for efficacy and safety in the single arm study;
- To examine the time-dependent time-to-event analysis for PFS, and AE events;
- To verify the prediction of hyperphosphatemia for different dose scenarios with hyperphosphatemia model.

19.4.3.2.2 Overview of Studies Included in E-R Analyses

Efficacy data from CBGJ398X2204 Cohort 1 were used for the E-R efficacy analyses of OR and PFS. The OR E-R analysis used predicted average daily infigratinib exposure measures and PFS E-R

NDA 214622 Multi-disciplinary Review and Evaluation
Infigratinib (Truseltiq)

analysis used daily PK exposure measures; these were estimated based on the population PK models for infigratinib. Data from CBGJ398X1101 (dose expansion cohorts), CBGJ398X2101 (dose expansion cohorts), CBGJ398X2201, and CBGJ398X2204 (Cohort 1) were used for the E-R analysis of safety (Table 68).

E-R model included the following:

- Logistic regression model for best OR (CR or PR)
- Cox proportional model for time to PFS
- Cox proportional model for AE (hyperphosphatemia, eye disorders, CSR/RPED, tissue calcification, and vascular calcification/mineralization)

Table 68. Studies Included for E-R Analyses.

Study Number/ Phase	Study Title	Participants Planned or Observed	Infigratinib Formulation/ Duration of Dosing	Planned Exclusions
CBGJ398X1101/ Phase 1	A phase I study of oral BGJ398 in Asian patients with advanced solid tumor having alterations of the FGF-R pathway	Planned Total: at least 33 Dose Escalation: at least 12 Chinese Safety Lead-in: at least 1 Dose Expansion: at least 20	CSF 28-day cycles continuous daily dosing Dose Escalation: proposed levels ranged from 50 to 200 mg QD or BID with 3 to 6 patients per level Chinese Safety Lead-in: equal or less than the maximum dose confirmed tolerable in Japanese patients with 3 to 6 new patients per level Dose Expansion: selected dose from Japanese Dose Escalation and Chinese Safety Lead-in; total of 20 Asian patients (at least 10 Chinese) or, if dose selected is race dependent, a total of 6 Japanese and 10 Chinese patients; this period can include additional patients or may be previously studied patients	Safety analyses only: Dose Escalation patients and patients without infigratinib PK exposures
CBGJ398X2101/ Phase 1	A phase I, open-label, multi-center, dose escalation study of oral BGJ398, a pan FGF-R kinase inhibitor, in adult patients with advanced solid malignancies	Observed Total: 208 Daily dosing for 28-day cycles: Dose Escalation: n = 43 Dose Expansion: n = 49 Dose Expansion (3 weeks on/1 week off): n = 116	CSF and FMI I formulations/ 28-day cycles continuous daily dosing Dose Escalation: 5, 10, 20, 40, 60, 100, and 125 mg QD and 50 mg BID Dose Expansion: 125 mg QD (2 treatment arms) 28-day cycles daily dosing (3 weeks on / 1 week off) Dose Expansion: 125 mg daily (2 additional treatment arms)	Safety analyses only: Dose Escalation patients and patients without infigratinib PK exposures
CBGJ398X2201/ Phase 2	A Phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable Glioblastoma	Planned Total: 34 Non-Surgical Group: n = 26 Surgical Group: n = 11	FMI I 28-day cycles daily dosing (3 weeks on /1 week off) 125 mg QD Surgical Group: 125 mg QD prior to surgery 28-day cycles beginning within 2 weeks postoperative	Safety analyses only: patients without infigratinib PK exposures
CBGJ398X2204/ Phase 2	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	Planned (data cutoff) Total: 71	FMI I or FMI III 28-day cycles daily dosing (3 weeks on /1 week off) 125 mg QD	OR and PFS analysis: patients without advanced or metastatic cholangio-carcinoma with FGFR2 gene fusions Safety and Efficacy: patients without infigratinib PK exposures

Abbreviations: BGJ398, infigratinib; BID, twice daily; CSF, clinical service form; FGF-R/FGFR, human fibroblast growth factor receptor; FMI I, final market image version 1; FMI III, final market image version 3; n, number of patients; OR, overall response; PFS, progression-free survival; PK, pharmacokinetic; QD, once daily.

^a Indicates ongoing clinical trial.

Source: <\\CDSESUB1\evsprod\NDA214622\0002\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\qed-pmx-002\qed-pmx-002.pdf> (page 67-68)

19.4.3.2.3 E-R Modeling for Efficacy

Exposure-efficacy model for BOR

In Study 2204, 108 patients were the target population with FGFR2 gene fusion/translocation. Among those, 64 patients with known BOR date and individual exposure measures were included in the E-R analysis. Baseline patient characteristics of the population PK dataset are summarized in Table 69.

Table 69. Summary of Baseline Demographic Characteristics in the Dataset by Last Dose.

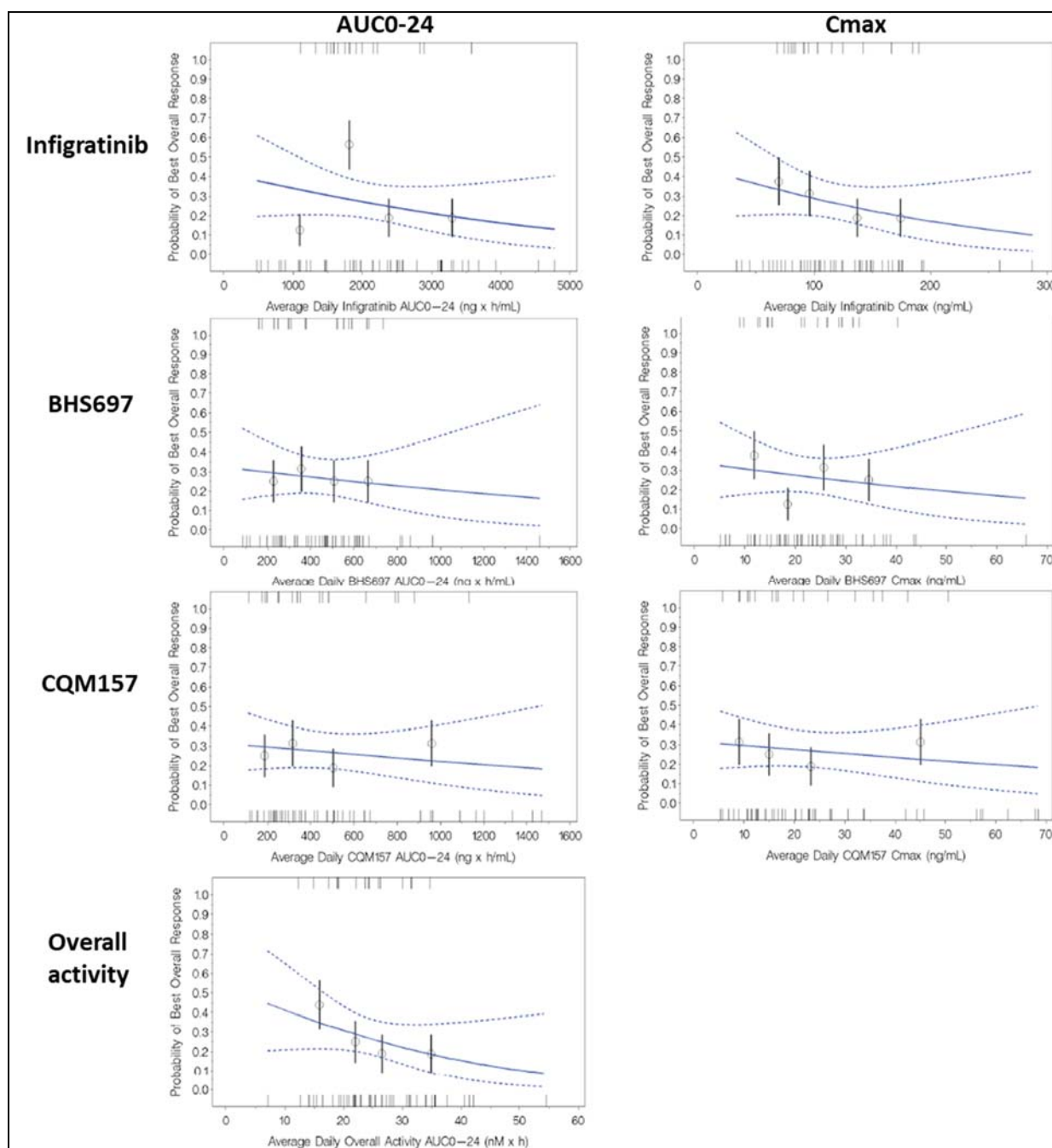
Characteristics	level	50 mg	75 mg	100 mg	125 mg	Total
N		5	18	19	22	64
Baseline ECOG, n (%)	0	3 (60.0)	10 (55.6)	7 (36.8)	12 (54.5)	32 (50.0)
	1	1 (20.0)	8 (44.4)	12 (63.2)	10 (45.5)	31 (48.4)
	2	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Lines of prior antineoplastic therapy, n (%)	No	2 (40.0)	8 (44.4)	4 (21.1)	11 (50.0)	25 (39.1)
	Yes	3 (60.0)	10 (55.6)	15 (78.9)	11 (50.0)	39 (60.9)
Race, n (%)	Caucasian	4 (80.0)	12 (66.7)	10 (52.6)	17 (77.3)	43 (67.2)
	Black	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	1 (1.6)
	Asian	1 (20.0)	2 (11.1)	4 (21.1)	2 (9.1)	9 (14.1)
	Other	0 (0.0)	1 (5.6)	1 (5.3)	1 (4.5)	3 (4.7)
	Unknown	0 (0.0)	3 (16.7)	4 (21.1)	1 (4.5)	8 (12.5)
Sex, n (%)	Male	2 (40.0)	7 (38.9)	5 (26.3)	11 (50.0)	25 (39.1)
	Female	3 (60.0)	11 (61.1)	14 (73.7)	11 (50.0)	39 (60.9)
Age (y), Mean (SD)		65.0 (13.2)	57.1 (13.9)	49.5 (14.8)	50.3 (10.9)	53.1 (13.7)
Weight (kg), Mean (SD)		75.4 (13.1)	70.1 (18.6)	74.7 (22.3)	75.9 (20.7)	73.9 (19.9)

Source: <\\CDSESUB1\evsprod\NDA214622\0002\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\qed-pmx-002\qed-pmx-002.pdf> (page 74)

The BOR response was modeled via logistic regression of linear combination of exposures and variables of interest. The following exposure measures were evaluated: C_{trough} , C_{max} , C_{avg} , and AUC_{0-24h} at steady state, and the corresponding average values till BOR. Average overall activity AUC_{0-24h} and C_{max} were selected to represent E-R relationship for the parent drug and metabolites in this review (Figure 17).

No covariate effect attributed by patient factors (e.g. age, weight, ECOG, etc.) was identified. There was no clear relationship between exposure measures of metabolites and OR. For the parent drug, either a negative trend or a bell shape curve was observed. The linear or quadratic trend was not statistically significant, suggesting that a larger exposure may not provide a better response.

Figure 17. Model-predicted Probability of Overall Response versus Exposures Overlaid with Observed Data.

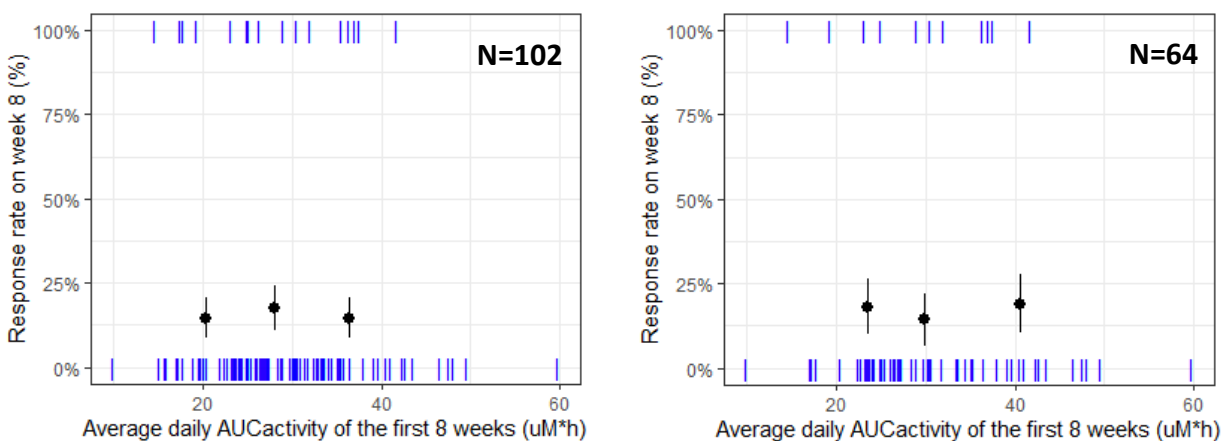


Source: \\CDSESUB1\evsprod\NDA214622\0002\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\qed-pmx-002\qed-pmx-002.pdf (page 141)

Relationship between early exposure and early response at Week 8

The relationship between early infigratinib exposure and early response at ~week 8 was explored by the reviewer to further assess if a high early exposure is critical for efficacy based on early response. The exposure was an average daily AUC_{activity} of the first 2 cycles (8 weeks) of treatment. No evident exposure-response was observed (Figure 18).

Figure 18. Week 8 Response Rate Versus Early Exposure Overlaid with Observed Data.



Note: The data with 102 subjects includes 38 patients whose exposure were simulated based on PopPK model with any individual exposure measure. The data with 64 subjects is a subset of the large dataset which included subjects with individual exposure measures only.

Source: Reviewer's analysis

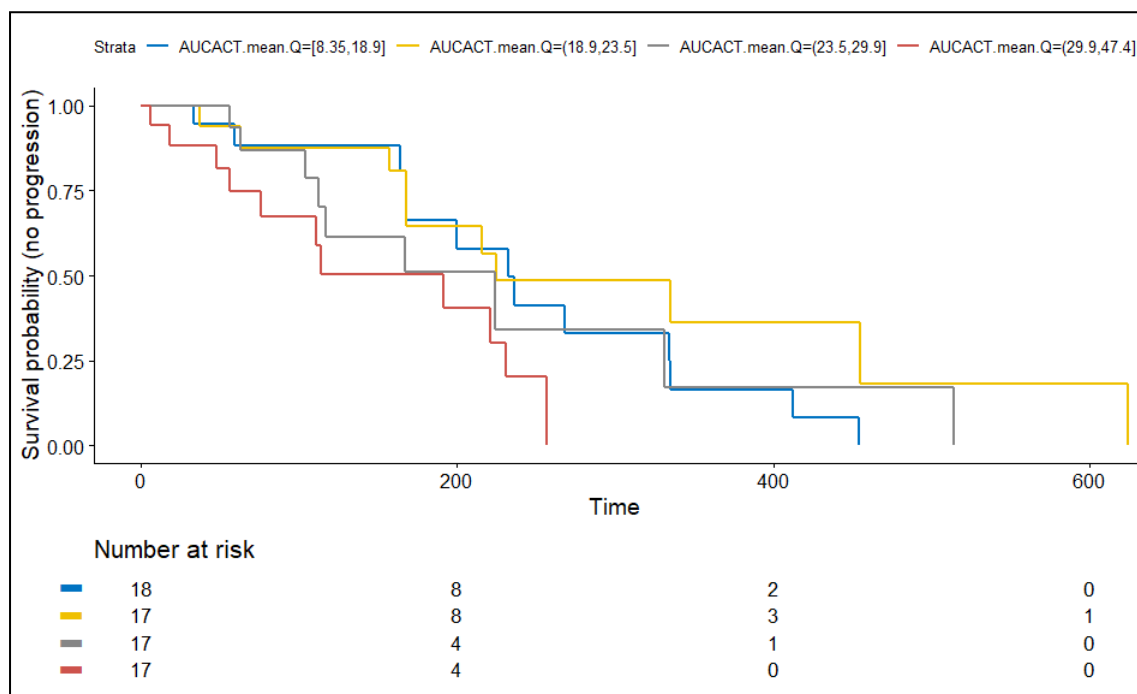
Cox proportional hazard model for PFS

Out of 108 patients with FGFR2 gene fusion/translocation in Study 2204, 69 patients with individual exposure measures were included in the E-R analysis. The dataset was expanded to daily records for each patient for time-dependent time-to-event analysis which included 12,056 daily records.

For the patients who experienced progression, the median days to the event was 170 days and ranged from 35 days to 636 days. Relationship between exposure measures of the parent/metabolites and PFS was not statistically significant. To show the probability of PFS between two AUC quantiles, sponsor generated "KM plots" in the report. We noted an increase in the number of patients at risk for either AUC quantile in the risk table under the "KM curve" (see Fig 7 in EDR 5.3.4.2 Study QED-PMX-002 report). This is because the "KM curves" were generated with all longitudinal records and each daily record of a subject was treated as an independent subject, thus the quantiles were split among all AUC records including repeated measures which introduced bias towards patients who had longer PFS. To address this issue, we summarized average daily overall activity AUC till the PFS event or censoring time to ensure one record/subject and generated a KM plot to visualize the probability of PFS over time. KM curves

were stratified by 4 quartiles of average daily overall activity AUC till the time of PFS event. As shown in Figure 19, the 4th quartile of AUC showed a worse PFS compared to the other quartiles even at earlier time points, suggesting that a higher exposure may not provide a better response.

Figure 19. Probability of PFS by Exposure Quartiles.



Source: Reviewer's analysis

Overall, with a limited sample size, a negative trend or bell-shaped of E-R curve was observed for both BOR and PFS. However, due to frequent dose interruption and reduction, as well as treatment discontinuation caused by exposure-related AE, the confounding issues in the E-R analyses could not be avoided, likely resulting in a biased E-R relationship. In addition, daily AUC in time-dependent time-to-event analysis for PFS may not be relevant to address chronological drug effect. Together, such analyses were only exploratory, and the concluded flat exposure-response may not be accurate.

19.4.3.2.4 E-R Modeling for Safety

Data used for exposure-safety analysis

Safety E-R analysis was performed on the pooled data from multiple studies summarized in the Table 11, which included first occurrence of first AE events (hyperphosphatemia, eye disorder, and CSR/RPED) from 368 patients. A total of 1840 AE observations from 368 patients were expanded to 227851 daily records (hyperphosphatemia, eye disorder, and CSR/RPED daily records individually listed). Out of the 368 patients, 300 patients with PK observations were used for the main exposure-safety analysis.

Baseline patient characteristics of the population PK dataset are summarized in Table 70. With respect to demographic characteristics, the distributions across the studies were generally similar except FGFR2 gene fusions/translocations which was 100% in the pivotal study.

Table 70. Summary of Baseline Demographic Characteristics from Patients with Pharmacokinetic observations in the Dataset by Study.

Characteristics	level	CBGJ398X11 01	CBGJ398X21 01	CBGJ398X22 01	CBGJ398X2 204	Total
N		9	188	24	79	300
Disease category, n (%)	Solid tumors	9 (100)	188 (100)	0 (0.0)	0 (0.0)	197 (65.7)
	Glioblastoma	0 (0.0)	0 (0.0)	24 (100)	0 (0.0)	24 (8.0)
	Cholangiocarcinoma	0 (0.0)	0 (0.0)	0 (0)	79 (100)	79 (26.3)
Baseline ECOG, n (%)	0	3 (33.3)	82 (43.6)	6 (25.0)	35 (44.3)	126 (42.0)
	1	6 (66.7)	94 (50.0)	10 (41.7)	43 (54.4)	153 (51.0)
	2	0 (0.0)	12 (6.4)	8 (33.3)	1 (1.3)	21 (7.0)
Tumor genetics, n (%)	Other FGFR genetic alterations	0 (0.0)	0 (0.0)	0 (0.0)	8 (10.1)	8 (2.7)
	FGFR2 Gene	0 (0.0)	0 (0.0)	0 (0.0)	71 (89.9)	71 (23.7)
	Fusions/Translocations					
	Unknown	9 (100.0)	188 (100.0)	24 (100.0)	0 (0.0)	221 (73.7)
Number of prior	0	0 (0.0)	43 (22.9)	12 (50.0)	28 (35.4)	83 (27.7)
antineoplastic therapy, n (%)	1	9 (100.0)	145 (77.1)	12 (50.0)	51 (64.6)	217 (72.3)
Phosphate binder, n (%)	Absent	8 (88.9)	117 (62.2)	13 (54.2)	38 (48.1)	176 (58.7)
	Present	1 (11.1)	71 (37.8)	11 (45.8)	41 (51.9)	124 (41.3)
Race, n (%)	Caucasian	0 (0.0)	160 (85.1)	24 (100.0)	53 (67.1)	237 (79.0)
	Black	0 (0.0)	3 (1.6)	0 (0.0)	2 (2.5)	5 (1.7)
	Asian	9 (100.0)	14 (7.4)	0 (0.0)	12 (15.2)	35 (11.7)
	Other	0 (0.0)	7 (3.7)	0 (0.0)	4 (5.1)	11 (3.7)
	Unknown	0 (0.0)	4 (2.1)	0 (0.0)	8 (10.1)	12 (4.0)
Sex, n (%)	Male	8 (88.9)	100 (53.2)	16 (66.7)	33 (41.8)	157 (52.3)
	Female	1 (11.1)	88 (46.8)	8 (33.3)	46 (58.2)	143 (47.7)
Age (y), Mean (SD)		56.3 (13.2)	60.2 (11.4)	53.6 (14.0)	53.8 (13.2)	57.9 (12.5)
Weight (kg), Mean (SD)		65.3 (14.2)	73.2 (19.3)	74.9 (17.4)	73.1 (19.6)	73.1 (19.1)
Phosphate (mg/dL), Mean (SD)		3.43 (0.45)	3.37 (0.57)	3.27 (0.49)	3.34 (0.59)	3.36 (0.56)

Hyperphosphatemia Cox proportional hazard model

Final Model

Overall, 72.7% of patients experienced hyperphosphatemia and 27.3% were censored. For the patients who experienced hyperphosphatemia, the median days to the event was 8 days and ranged from 1 day to 141 days. An apparent E-R relationship was identified where a higher overall activity AUC was associated with a higher probability of hyperphosphatemia.

Apart from exposure, co-administration of phosphate binders and high baseline phosphate were found to increase the probability of hyperphosphatemia. Given hyperphosphatemia is an on-

target effect of FGFR inhibitors, phosphate binders were used in 81% of patients either prophylactically in early phase of Study 2204 (protocol amended to remove requirement for prophylactic use, 48% of patients), or to manage of hyperphosphatemia during treatment (32% of patients). Therefore, the increased risk of hyperphosphatemia with phosphate binder is likely a confounding effect rather than a predictor for hyperphosphatemia.

Confounding effect of phosphate binder usage in E-R analysis for hyperphosphatemia

Given a large increase in the probability of hyperphosphatemia (~20%) in the presence of phosphate binder predicted by sponsor's model, we recommended sponsor to check the analysis and perform analysis in patients without prophylactic usage of phosphate binder.

In IR response submitted on 1/11/2021 (20210111_FDA_NDA_RFI_Clin Pharm Response_AC), phosphate binder was still identified as a covariate, suggesting that the confounding issue remained unaddressed. Sponsor carried out time to first event of hyperphosphatemia analysis using Cox regression with time-dependent covariates. The setup of the data however is problematic for time-dependent analysis in that 52 patients out of 293 patients had phosphate binder usage concurrent with the first event of hyperphosphatemia. According to the protocol, patients who experienced abnormal phosphate level (>5.5 mg/dL) during infigratinib treatment were given phosphate binder to manage the hyperphosphatemia. In other words, the occurrence of hyperphosphatemia should precede the usage of phosphate binder. The R program for Cox model takes the values of the covariates on the same row of the event, hence identified the resultant phosphate binder usage as a predictor for hyperphosphatemia event.

Reviewer's independent time-to-event analysis for hyperphosphatemia and simulation

To address the confounding issue with phosphate binder usage, the reviewer carried out sensitivity analysis. The last value of phosphate binder of each subject was supplanted with the previous value (one day prior), and the new variable was used in the Cox regression. The updated phosphate binder usage was no longer identified as a covariate in univariate or multivariate analysis. Thus, the final model was modified to exclude phosphate binder usage as described below:

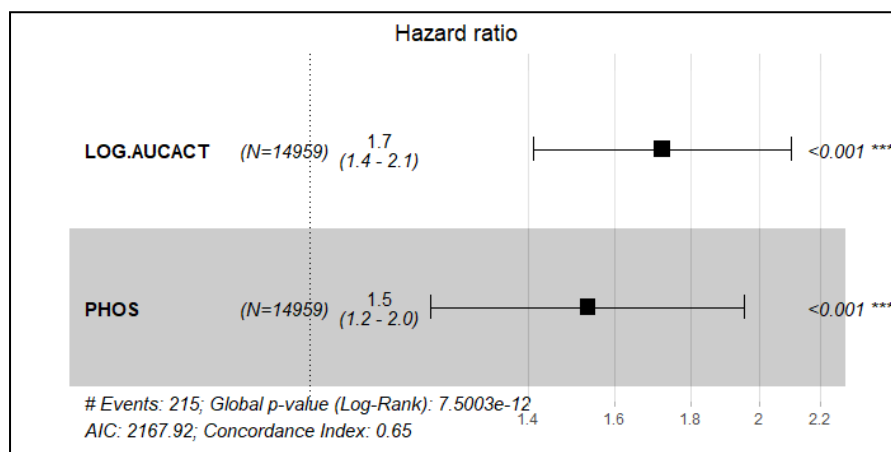
$$h(t) = h_0(t) * \exp(a * \log(AUC_{activity}) + b * PHOS_{baseline})$$

Where $h_0(t)$ is baseline hazard, a is the coefficient for overall activity AUC_{0-24h} , b is the coefficient for baseline phosphate level, t is time in days.

The coefficient for $\log(AUC_{activity})$ was estimated to be 0.5437, which means for each increase of 1 $\mu M \cdot h$ of log-transformed overall activity AUC, the predicted hazard for hyperphosphatemia was increased by 70% (Figure 20). Using the geomean of simulated AUC for different doses (44.7, 35.8, 26.9, 18 $\mu M \cdot h$ for 125, 100, 75, and 50 mg, respectively), the hazard ratio for hyperphosphatemia is predicted to be 88.6%, 75.9%, and 61% for 100, 75, and 50 mg dose relative to 125 mg dose. Of note, the analysis included patients who were on prophylactic

phosphate binder which was not identified as a covariate possibly due to variability, therefore the impact of exposure on probability of hyperphosphatemia remains underestimated.

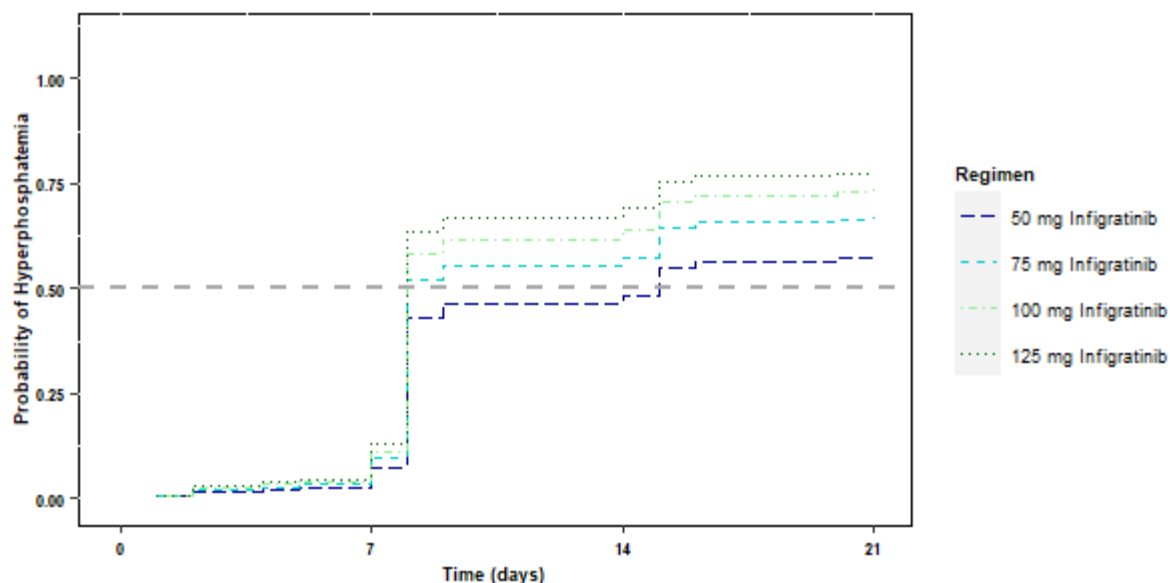
Figure 20. Hazard Ratio of Significant Covariates for Final Hyperphosphatemia Model.



Source: Reviewer's analysis

Stochastic simulation with the final reviewer's model was carried out following sponsor's approach. Individual daily exposures up to 20 days for doses of 50 mg, 75 mg, 100 mg, and 125 mg were generated by applying sponsor's final PK models. The exposure and baseline phosphate level of 3.4 mg/dL was used for prediction of hyperphosphatemia event. To account for the multiple records per subject, we specified argument id in survfit function to predict survival probability (1-probability of hyperphosphatemia) over time for individuals. Median, 2.5th, and 97.5th percentile of the probability for hyperphosphatemia by day were summarized and plotted (Figure 21). Compared to sponsor-predicted reduction in probability of hyperphosphatemia for 100, 75, and 50mg dose (3.3%, 7.8%, 14.5%), the magnitude of reduction was larger (4%, 9.4%, 17.1%) in the reviewer's analysis after correcting the data organization issue.

Figure 21. Predicted Probability of Hyperphosphatemia at 50, 75, 100, and 125 mg.



Source: Reviewer's analysis

Eye disorder Cox proportional hazard model

Overall, 52.2% of patients experienced eye disorders (excluding CSR/RPED) and 47.8% were censored. For the patients who experienced eye disorders, the median days to the event was 22 days and ranged from 1 day to 224 days. A positive E-R relationship was identified. The issues regarding KM plot were discussed in previous section.

CSR/RPED Cox proportional hazard model

No relationship was identified between infigratinib exposure and CSR/RPED event.

Overall, no clear E-R relationship was found between infigratinib exposure and efficacy endpoints. In contrast, a higher exposure is associated with a higher rate of hyperphosphatemia and eye disorder. Taken together, the current analysis did not fully support 125mg to be the optimal dose from efficacy and safety standpoint.

19.4.5. Pharmacogenomic Exploratory Analysis

FGFR2 Alterations and Treatment Response in Study CBGJ398X2204:

Patient Selection: The detection of FGFR2 fusions or other rearrangements in tumor tissue by either local or central test was required to determine molecular eligibility. Of 108 patients comprising the efficacy population, 89% (n=96) were enrolled based on local tests (DNA-based NGS (n=59), RNA-based NGS (n=25), PCR (n=3), Break Apart FISH (n=9) and 11% (n=12) were

enrolled based on a central NGS test (FoundationOne T7). Tumor samples of 78% (75/96) of patients enrolled based on local tests were retrospectively evaluated with the central test. Of these, a FGFR2 fusion or other rearrangement was detected in 48 samples. For the remaining 27 samples, 8 were negative for FGFR2 alterations, and 19 failed test requirements. Because central test results were not available for approximately 37% of patients in the study, exploratory analyses presented below considered fusions vs. other rearrangements categorization as reported by the Applicant for enrollment, except for 9 patients enrolled based on FISH, where available central results were used.

Distribution of FGFR2 fusions or other rearrangements: According to the central test classification rules, both FGFR2 fusions and other rearrangements have the breakpoint within the FGFR2 intron 17/ exon 18 hotspot. For rearrangements predicted to be fusions, the fusion gene partner is known in the literature, in strand with FGFR2; or is a novel partner that is predicted to be in strand and in frame with FGFR2. For those not predicted to be fusions, the partner gene is out of frame or out of strand with exon 17 of FGFR2. In addition, the downstream end of the breakpoint may be in an intergenic region and not within another gene. Cases where the assay pipeline could not decide were classified as non-fusion rearrangements. The Applicant indicated that 60% of local tests used definitions consistent with the central test. For the remaining tests, definitions were not available, or the test could not distinguish or indicate partner (FISH).

A total of 106 patients (of 108) had tumors positive for either an FGFR2 fusion (n=88) or other rearrangement (n=18) as determined by local and/or central test (Table 71), most (104) of which were NGS-based. For 2 patients enrolled based on FISH and with failed central retesting, distinction could not be made (Table 71).

Table 71: Distribution of FGFR2 Fusions or other Rearrangements per Local and/or Central Testing (N=108)

FGFR2 Alteration Type	Local tests (enrollment)	Central test (enrollment)	Total
Fusion	74	9	83 (+5)
Rearrangement	13	3	16 (+2)
Unknown (FISH) *	9	----	(2) ^{&}
Total	96	12	108

Source: Reviewer analysis based on fgfrnda dataset. * Unknown whether is a fusion or other (non-fusion) rearrangement. Tumor samples of 9 patients enrolled based on FISH results were centrally retested. Of these, 7 were reclassified as having fusions (n=5) or other rearrangements (n=2). [&]Two samples failed central testing, and status remained unknown. Central test results of samples of patients enrolled based on FISH are indicated in parenthesis.

In the subset of FGFR2 fusions (n=88), 46 different partners were identified, most (n=36) occurring only once. BICC1 was the most common fusion partner (n=27), consistent with the literature. The distribution of FGFR2 fusions and other rearrangements is presented in Table 72.

Table 72: FGFR2 Fusions and other Rearrangements in Study CBGJ398X2204 (N=106)

FGFR2 Fusions (n=88)	Number of Patients
FGFR2-BICC1	27
FGFR2-AHCYL1	4
FGFR2-KIAA1217	4
FGFR2-CCDC6	3
FGFR2-SHTN1	3
FGFR2-WAC	3
FGFR2-NRAP	2
FGFR2-PAWR	2
FGFR2-PHLDB2	2
FGFR2-RBM20	2
Other FGFR2 partners, one patient each ¹	36
Other FGFR2 Rearrangements (n=18)	Number of Patients
Partner identified ²	6
FGFR2 intron 17 (N/A) / partner not identified ³	12

Source: Reviewer analysis based on fgfrnda dataset. Distributions reflect local or central test results as obtained for enrollment, except for patients enrolled based on FISH, where central results were used. Two patients with unknown status are not included. HUGO Gene Nomenclature Committee (HGNC) symbols were used to represent gene partners. In response to an FDA information request (03/10/2021), the applicant identified four fusions with FGFR2 as the 3' partner gene (5' partners RBM20 (n=2), ANKRD13C (n=1), and STMP1 (n=1)) based on information listed within the local test reports. No central confirmation of whether these corresponded to 3' FGFR2 fusions was available. Two of the patients achieved a PR by BICR. Of note, a breakpoint within the FGFR2 intron 17/exon 18 hotspot with FGFR2 as the 3' partner gene would predict exclusion of the kinase domain from the fusion protein.

1. FGFR2 fusion partners identified once (N=36): AFF1, AFF4, AHCYL2, ANKRD13C, CCDC186, CCDC147, CELF2, CREM, DNAJC12, ERC1, ETV6, FOXP1, GAB1, HOOK1, ITHI2, KCTD1, KHDRBS1, KIF3, MYPN, NOL4, PCM1, PDE3B, PPP1R21, RASAL2, SG3GLB1, SHROOM3, SLMAP, SORBS1, STK3, STMP1, TNS1, TRIM8, UBQLN1, USO1, VCL, and ZMYM4.
2. FGFR2 [Non-fusion] rearrangement partners (n=6): ALDH1L2, DEXI, PHF7, RNF213, ROBO2, and VCL.
3. Includes 1 patient with FGFR2 amplification exons 1-16 (local)/FGFR2- ARFIP1 rearrangement (central) and 1 patient with FGFR2 intron 17 (local) and FGFR2-PAWR fusion (central).

Exploratory analyses of response by FGFR2 alteration type: Confirmed responses (CR or PR) were observed in patients with tumors having FGFR2 fusions (ORR 23.9%; 95% CI: 15.4, 34.1) or other rearrangements (ORR 22.2%; 95% CI: 6.4, 47.6) (Table 73). FGFR2-BICC1 was the most common fusion among responders (n =9). All other fusions identified in responders were unique. FGFR2 rearrangement intron 17 was identified in 3 of 4 responders with non-fusion rearrangements. Of note, fusions that are in-frame and predicted to have an intact kinase domain suggest potential functionality. Although detected in tumor samples, it is unclear

whether other FGFR2 rearrangements produce active kinases. A few patients were noted to have other alterations in FGFR2 in addition to fusions or other rearrangements, including 2 patients with point mutations (FGFR2 p.R678G and p.L654T, one each), 2 patients with FGFR2 amplification and one patient with FGFR2 overexpression. No responses (CR or PR) by BICR were observed in this group of patients.

Table 73: BICR-Assessed Responses in Patients with FGFR2 Fusions or other Rearrangements in Study CBGJ398X2204 (N=108)

Efficacy Parameter	Fusion (n= 88)	Rearrangement (n=18)	Unknown * (n=2)	Total (N=108)
ORR (CR+PR) n (%)	21 (23.9; 95% CI:15.4, 34.1)	4 (22.2; 95% CI: 6.4, 47.6)	(0)	25 (23.1; 95% CI: 15.6, 32.2)
Complete Response (CR)	1	0	0	1
Partial Response (PR)	20	4	0	24
Progressive Disease (PD)	8	3	1	11
Stable Disease (SD)	54	12	1	66
Not Done	5	1	0	6

Source: Reviewer's exploratory analysis based on fgfrnda and adef datasets ORR= overall response rate; BICR= blinded independent central review: Data are according to RECIST v1.1 *Unknown whether is a fusion or other (non-fusion) rearrangement

As part of the CBGJ398X2204 study, investigators could submit a post-progression tumor biopsy for central testing to support the exploratory objective aimed at identifying mechanisms of resistance to infigratinib. In response to an FDA information request (12/10/2020), the Applicant indicated that FGFR2 kinase domain mutations (p.N549K and p.V564L) were identified in post-progression tissue biopsies of 2 patients out of 4 patients tested. These 2 patients were enrolled based on samples positive for FGFR2 rearrangement (RNF213 partner) and fusion (RBM20 partner) respectively and had SD as best overall response by BICR (PR by investigator). Mutations at residues N549 and V564 (gatekeeper) of FGFR2 have been associated with resistance to FGFR inhibitors (Goyal et al. 2017, Silverman et al. 2021), reiterating the importance of investigating mechanisms of primary and acquired resistance during development. A PMC will be requested (See Section 13 for details).

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

No additional safety analyses were conducted.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Denali (Dubravka) Kufrin	OOD/DHOT	Sections: 5 and 19.3	Select one: ☒ Authored ☐ Approved
Signature: Denali D. Kufrin -S Digitally signed by Denali D. Kufrin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300403796, cn=Denali D. Kufrin -S Date: 2021.05.19 09:08:02 -04'00'				
Nonclinical Team Leader	Matthew Thompson	OOD/DHOT	Sections: 5 and 19.3	Select one: ☒ Authored ☒ Approved
Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001270689, cn=Matthew D. Thompson -S Date: 2021.05.20 07:01:21 -04'00'				
Nonclinical Division Director	John Leighton	OOD/DHOT	Sections: 5 and 19.3	Select one: ☐ Authored ☒ Approved
Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2021.05.19 08:34:20 -04'00'				
Clinical Pharmacology Reviewer	Lili Pan	OTS/OCP/DCP II	Sections: 6 and 19.4	Select one: ☒ Authored ☐ Approved
Signature: Lili Pan -S Digitally signed by Lili Pan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lili Pan -S, 0.9.2342.19200300.100.1.1=2001832999 Date: 2021.05.19 08:39:10 -04'00'				
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach	OTS/OCP/DCP II	Sections: 6 and 19.4	Select one: ☒ Authored ☒ Approved
Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300434575, cn=Jeanne Fourie Zirkelbach -S Date: 2021.05.24 10:15:41 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.05.24 11:04:02 -04'00'			
Pharmacometrics Reviewer	Ye Xiong	OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ye Xiong -S, 0.9.2342.19200300.100.1.1=2003112200 Date: 2021.05.20 09:45:38 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	OTS/OCP/DPM	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.05.20 09:22:57 -04'00'			
Genomics Reviewer	Oluseyi Adeniyi	OTS/OCP/DTPM	Sections: 6 and 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Oluseyi Adeniyi -S Digitally signed by Oluseyi Adeniyi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001901490, cn=Oluseyi Adeniyi -S Date: 2021.05.19 10:51:21 -04'00'			
Genomics Team Leader	Rosane Charlab Orbach	OTS/OCP/DTPM	Sections: 6 and 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2021.05.19 16:47:57 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Lorraine Pelosof	OOD/DO3	Sections: 1.4, 2, 3, 4, 7, 8, 9, 10, 12, 13, 19.1, 19.2	Select one: ☒ Authored ☐ Approved
	Signature:  Lorraine Pelosof -S Digitally signed by Lorraine Pelosof -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001855909, cn=Lorraine Pelosof -S Date: 2021.05.20 11:16:55 -04'00'			
Statistics Reviewer	Abhishek Bhattacharjee	OB/DBV	Sections: 8.1, 8.3	Select one: ☒ Authored ☐ Approved
	Signature: <i>Team Leader Joyce Cheng signing on behalf of Abhishek Bhattacharjee</i>  Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2021.05.24 10:38:49 -04'00'			
Statistics Team Leader	Joyce Cheng	OB/DBV	Sections: 8.1, 8.3	Select one: ☒ Authored ☒ Approved
	Signature:  Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2021.05.24 10:31:47 -04'00'			
Statistics Division Director	Shenghui Tang	OB/DBV	Sections: 8.1, 8.3	Select one: ☐ Authored ☒ Approved
	Signature:  Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.05.24 10:21:19 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OOD/IO	Sections: 11	Select one: ☒ Authored ☒ Approved
	Signature:  Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093094, cn=Barbara A. Scepura -S Date: 2021.05.24 10:44:35 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader/ Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	OOD/DO3	Authored Section: 1, 4, 10, 11, 13 Approved Section: All	Select one: ☒ Authored ☒ Approved
	Signature: Refer to final assessment aid.			
Division Director (Clinical)	'Lola Fashoyin-Aje	OOD/DO3	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: Refer to final assessment aid			

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
05/27/2021 12:11:26 PM

SANDRA J CASAK
05/27/2021 01:50:19 PM

IBILOLA A FASHOYIN-AJE
05/27/2021 01:51:17 PM

PAUL G KLUETZ
05/27/2021 02:58:22 PM