# Infigratinib (BGJ398)
# Abbreviated Clinical Study Report QBGJ398-302:
# Final Analysis

## 1. TITLE PAGE

### Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302)

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| **Indication:** | Urothelial Carcinoma |
| **Phase of Development:** | 3 |
| **First Subject First Dose:** | 18 March 2020 |
| **Last Subject Last Dose:** | 10 November 2022 |
| **Date of Report:** | 02 August 2023 |
| **Sponsor's Responsible Medical Officer:** | David van Veenhuyzen, MBChB, MPharmMed |
| **Study Medical Monitor:** | David van Veenhuyzen, MBChB, MPharmMed |
| **Sponsor:** | QED Therapeutics, Inc.<br>1800 Owens Street, Suite C-1200<br>San Francisco, CA 94158 |
| **EudraCT Number:** | 2019-003248-63 |
| **Clinical Trials Identifier:** | NCT04197986 |

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline, including the archiving of essential documents.

# 2. SYNOPSIS

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| **Name of Sponsor/Company:** QED Therapeutics, Inc. | Individual Study Table Referring to Part of the Dossier<br>Volume: NA<br>Page: NA | *(For National Authority Use Only)* |
| **Name of Investigational Product:** Infigratinib (formerly BGJ398, also known as BBP-831 and infigratinib phosphate) | | |
| **Name of Active Ingredient:** Infigratinib | | |
| **Title of Study:** Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Infigratinib for the Adjuvant Treatment of Subjects with Invasive Urothelial Carcinoma with Susceptible FGFR3 Genetic Alterations (PROOF 302) | | |
| **Study Centers:** Subjects were enrolled across 30 study centers (11 in North America, and 19 in Western Europe). | | |
| **Publication (reference):** None | | |
| **Study and Reporting period:**<br>Date first subject treated: 18 March 2020<br>Date of data cutoff for the primary analysis: 28 Feb 2023<br>Last subject, last dose for the study: 10 Nov 2022 | **Phase of development:** 3 | |

**Background and Rationale for the Study:**

In 2018, it was estimated that over 150,000 people would be diagnosed with urinary system cancer. More than half (~54%) would be diagnosed with cancers of the urinary bladder and the remainder diagnosed with cancers of the kidney and renal pelvis (~43%), and of the ureter and other urinary organs (<3%) (Siegel 2018). Urothelial carcinoma (transitional cell carcinoma) is by far the most common type of urinary system cancer (Kaseb 2022).

At the time of diagnosis, approximately 20% of patients with urothelial carcinoma have invasive urinary bladder cancer (UBC) (Roupret 2015). Invasive UBC has a poor prognosis; approximately 50% of patients will develop metastatic disease and the 5-year mortality is approximately 50% (Knowles 2015). Approximately 5% to 10% of patients with urothelial carcinomas are diagnosed with upper tract urothelial carcinomas (UTUC; transitional cell carcinoma of the ureter or renal pelvis). At the time of diagnosis, 60% of patients with UTUC have invasive cancer compared to 15% to 25% of patients with UBC (Margulis 2009; Roupret 2015). In contrast to invasive UBC, UTUC has a more aggressive clinical course. Thirty-six percent (36%) have regional disease and 9% have distant disease (Raman 2010). A large retrospective review of patients with UTUC who underwent radical nephroureterectomy (RNU) demonstrated that 28% of the total population had recurrence outside of the bladder after surgery (Margulis 2009). The 5-year survival rate (overall death rate) is likely much higher than 50% (Roupret 2018).

Standard-of-care neoadjuvant, adjuvant, and metastatic disease treatment is based on urothelial histology common to UBC and UTUC. Most commonly, neoadjuvant and adjuvant treatment regimens containing cisplatin in combination with other cytotoxic agents are administered for 3 to 4 cycles. However, there remains a need for alternative treatment options.

For patients with invasive UBC, a survival benefit has been demonstrated for neoadjuvant cisplatin-based chemotherapy; however, patients with residual disease following neoadjuvant therapy have a poor prognosis (Grossman 2003). In addition, studies suggest that patients with invasive UBC are unlikely to

receive neoadjuvant or adjuvant cisplatin-based chemotherapy, in part due to cisplatin ineligibility (Porter 2011). Postoperative complications can also preclude the use of adjuvant cisplatin-based therapy for patients with invasive UBC (Donat 2009).

For patients with UTUC, the use of standard-of-care adjuvant platinum-based chemotherapy was supported by the POUT trial, a large, randomized trial in UTUC (Birtle 2020). In this study, a gemcitabine-platinum combination chemotherapy initiated within 90 days after RNU significantly improved disease-free survival (DFS) in patients with locally advanced UTUC. However, renal function before and after RNU greatly limits the number of patients with UTUC who are eligible for platinum-based neoadjuvant or adjuvant therapy (Lane 2010).

The fibroblast growth factor receptor (FGFR) family of receptors (FGFRs 1-4) serve as the high-affinity receptors for 22 FGF ligands. These are pleiotropic growth factors that control cell proliferation, migration, angiogenesis, apoptosis, and differentiation and are involved in both developmental and adult tissue homeostasis. Several lines of evidence support the association and the involvement of FGFRs in human cancer, where genetic alterations leading to abnormal activation and/or deregulated expression of FGFs and FGFR family members has been found in diverse tumor types. Somatic activating mutations in FGFR3 have been identified in solid tumors, with high frequency in bladder carcinomas (Cappellen 1999), where FGFR3 overexpression is also reported (Tomlinson 2007). Activating point mutations of FGFR3 have been identified in approximately 40% of bladder tumors overall. Eleven different missense mutations in Exons 7, 10 and 15, have been identified (Knowles 2008). Some of these mutations lead to constitutive activation of the kinase activities of the receptor and downstream signaling, and activation of FGFR family members occurs also as fusion proteins that result from chromosomal rearrangements (eg, translocations) with other genes (Katoh 2019). FGFR3 alterations occur in up to two-thirds of patients with UTUC (Sfakianos 2015; Moss 2017; Bagrodia 2019).

Infigratinib is an orally bioavailable, potent, and selective adenosine triphosphate (ATP)-competitive inhibitor of FGFRs 1-3, which has demonstrated anti-tumor activity in nonclinical in vitro and in vivo tumor models harboring FGFR genetic alterations. Evidence of clinical activity and a predictable, acceptable, and manageable on-target safety profile have been observed in adult patients with advanced solid malignancies and in patients with unresectable locally advanced or metastatic cholangiocarcinoma demonstrating the potential for infigratinib to treat serious and life-threatening disease in a population with refractory disease.

The purpose of this study was to evaluate the efficacy of infigratinib relative to placebo in subjects with invasive urothelial carcinoma (invasive UTUC or UBC) with susceptible FGFR3 alterations who are within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for or refuse cisplatin-based adjuvant chemotherapy or with residual disease following neoadjuvant therapy.

**Overview of Study Design:**

Study QBGJ398-302 (the PROOF 302 trial) was a Phase 3 multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy of infigratinib in approximately 218 adult subjects with invasive urothelial carcinoma with susceptible FGFR3 genetic alterations (mutations, and gene fusions or rearrangements; hereafter referred to collectively as “FGFR3 alterations”) who were within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy, and ineligible for or refused cisplatin-based (neo)adjuvant chemotherapy, or with residual disease after neoadjuvant therapy. Subjects with invasive urothelial carcinoma includes subjects with invasive UTUC or UBC.

Subjects were randomly assigned (1:1) to receive oral infigratinib or placebo administered once daily for the first 3 weeks (21 days) of each 28-day cycle for a maximum of 52 weeks (13 cycles), or until local/regional or contralateral invasive or metastatic recurrence (whichever occurred first) was confirmed by blinded independent central review (BICR), or until other criteria specified in the protocol were met, whichever occurred first.

Subjects were to be evaluated for tumor recurrence radiographically every 3 months for the first 24 months after the start of treatment, and annually thereafter or until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR already occurred. Cystoscopy (for subjects with a bladder) and urine cytology/cell-free DNA (cfDNA) was to be performed at 3, 6, 9, and 12 months, then every 6 months up to 24 months after start of treatment, and then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred. After metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR has already occurred, subjects were to be followed up for survival status and use of anticancer therapy approximately every 6 months (via phone or office visit) up to 1 year, then annually thereafter until 1 year after the final DFS event goal was reached (ie, end of study [EOS]).

**Objectives:**

**Primary:** To determine if treatment with infigratinib improves centrally reviewed DFS compared with placebo treatment of subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations after nephroureterectomy, distal ureterectomy, or cystectomy.

**Secondary:**

- To compare DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence in subjects treated with infigratinib vs placebo.
- To compare metastasis-free survival (MFS) of subjects treated with infigratinib vs placebo.
- To compare overall survival (OS) in subjects treated with infigratinib vs placebo.
- To compare investigator-reviewed DFS in subjects treated with infigratinib vs placebo.
- To characterize the safety and tolerability of infigratinib when administered as postoperative adjuvant monotherapy.

**Exploratory:**

A number of exploratory objectives were included in the protocol, however, due to early termination of the study, they were not evaluated. See Table 1 for further details.

**Endpoints**:

**Primary:** Centrally reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier.

**Secondary:**

- Investigator-reviewed DFS including intraluminal low-risk (noninvasive, low-grade, or high-grade) recurrence, from date of randomization to any recurrence or death due to any cause, whichever occurs earlier.
- Investigator-reviewed MFS, from date of randomization to metastatic recurrence or death due to any cause, whichever occurs earlier.
- OS (from date of randomization to death).
- Investigator-reviewed DFS, from date of randomization to local/regional or contralateral invasive or metastatic recurrence, or death due to any cause, whichever occurs earlier.
- Type, frequency, and severity of adverse events (AEs) and serious adverse events (SAEs), laboratory abnormalities, and other safety findings.

**Exploratory:**

A number of exploratory endpoints were included in the protocol, however, due to early termination of the study, they were not evaluated. See Table 1 for further details.

**Methodology:**

This was a multicenter, double-blind, randomized, placebo-controlled Phase 3 study to evaluate the efficacy of infigratinib in adult subjects with invasive urothelial carcinoma with susceptible FGFR3 alterations who were within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and ineligible for or refused cisplatin-based (neo)adjuvant chemotherapy, or who had residual disease following neoadjuvant therapy. Subjects with invasive urothelial carcinoma includes subjects with invasive UTUC or UBC.

Subjects were randomly assigned (1:1) to receive oral infigratinib 125 mg or placebo administered once a day for the first 3 weeks (21 days) of a 28-day treatment cycle. Randomization was stratified according to lymph node involvement, prior neoadjuvant cisplatin chemotherapy, Stage (pT2 vs >pT2), and disease (UTUC vs UBC).

Treatment in each cohort continued for a maximum of 52 weeks (13 cycles) or until local/regional or contralateral invasive or metastatic recurrence (whichever occurred first) was confirmed by BICR, or other prespecified criteria was met as per the protocol (Appendix 16.1.1).

Subjects were evaluated for tumor recurrence radiographically every 3 months for the first 24 months after the start of treatment, and annually thereafter or until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR had already occurred. Cystoscopy (for subjects with a bladder) and urine cytology/cfDNA was performed every 3 months up to the 12-month visit, then every 6 months up to 24 months after start of treatment, and then annually until metastatic recurrence by BICR or metastatic recurrence by investigator assessment if local/regional or contralateral invasive recurrence by BICR had already occurred. After metastatic recurrence, subjects were followed up for survival status and use of anticancer therapy approximately every 6 months (via phone or office visit) up to 1 year, then annually thereafter until 1 year after the final DFS event goal was reached (ie, EOS).

Due to sponsor decision this study was terminated earlier than the full survival period.

**Number of subjects (planned and analyzed):**

Approximately 218 subjects with histologically confirmed invasive urothelial carcinoma (invasive UTUC or UBC) with susceptible FGFR3 alterations within 120 days following nephroureterectomy, distal ureterectomy, or cystectomy and who were ineligible for or refused cisplatin-based adjuvant chemotherapy, or with residual disease following neoadjuvant therapy were planned for study participation. The sample size could be increased up to a total of 328 subjects based on interim analysis result using an adaptive design promising zone approach.

In total, 39 subjects were enrolled to the study and received at least 1 dose of study drug: 20 subjects in the infigratinib cohort and 19 in the placebo cohort.

**Diagnosis and main criteria for inclusion:**

**Main inclusion criteria:**

1. Are ≥18 years of age (≥20 years of age in Taiwan) of either sex.
2. Have signed informed consent.
3. Are randomized within 120 days following nephroureterectomy, distal ureterectomy or cystectomy. Note: at the time of definitive surgery, lymph node dissection (LND) should be performed in cases of suspected lymph node invasion based on preoperative imaging or intraoperative findings. In other cases, LND is to be performed in accordance with surgeon preferences/local standard practices.
4. Have histologically or cytologically confirmed, invasive urothelial carcinoma with susceptible FGFR3 alterations. Variant histology is allowed provided urothelial carcinoma is predominant

(>50%). Neuroendocrine (including small and large cell), sarcomatoid, and plasmacytoid variants are excluded (any component).

a. Regarding samples and documentation of FGFR3 alterations:
   i. FGFR3 mutation is confirmed if: FGFR3 gene is mutated in Exon 7 (R248C, S249C), Exon 10 (G370C, A391E, Y373C), or Exon 15 (K650M/T, K650E/Q)

   OR

   ii. FGFR3 gene fusion or FGFR3 rearrangement is confirmed based on the following genomic criteria if:
      (1) Any fusion/rearrangement with a literature-derived known partner gene regardless of strand or frame.
      (2) Fusion/rearrangements in the same strand that are in frame with a novel partner gene.
      (3) Fusion/rearrangements with one breakpoint in the intron 17 - exon 18 hotspot region and the other breakpoint in an intergenic region or another gene. This rule excludes 3′ duplications comprising only exon 18.
   iii. The amino acid numbers for the FGFR3 mutations refer to the functional FGFR3 isoform 1 (NP_000133.1) that is the National Center for Biotechnology Information (NCBI) Refseq ID used to report genetic alterations in FGFR3 by the FoundationOne® CDx test (F1CDx, Foundation Medicine, USA).
   iv. Written documentation of central laboratory determination by F1CDx of FGFR3 alterations is required for study eligibility.
   v. For subjects who require molecular prescreening to confirm the presence of the FGFR3 alteration to meet the inclusion criteria, a tumor sample with a pathology report must be sent to Foundation Medicine USA for F1CDx testing.
      (1) The tumor sample to be used should be from the definitive surgical resection (cystectomy, nephroureterectomy, or distal ureterectomy).
      (2) An archival biopsy of confirmed invasive urothelial carcinoma (≥pT2) can be used if (1) tissue from definitive surgery cannot be submitted, (2) the biopsy sample is not older than 4 months prior to surgery date and (3) the subject did not receive any type of systemic anticancer treatment since the biopsy was obtained. If more than one biopsy is available, the most recent one is to be sent.

b. If status post neoadjuvant chemotherapy, pathologic stage at surgical resection must be Stage ≥ ypT2 and/or yN+. Prior neoadjuvant therapy is defined as at least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m$^2$/cycle. Subjects who received less than this or non-cisplatin-based neoadjuvant treatment are not excluded. If enrolled, they will be stratified as having received no neoadjuvant chemotherapy.
c. If not status post neoadjuvant chemotherapy, is ineligible to receive cisplatin-based adjuvant chemotherapy based on Galsky (2011):
   i. Creatinine clearance ≤60 mL/minute, or
   ii. Common Terminology Criteria for Adverse Events (CTCAE version 5.0) Grade ≥2 hearing loss, or
   iii. CTCAE Grade ≥2 neuropathy.
d. Subjects who refuse cisplatin-based chemotherapy or who are ineligible to receive cisplatin-based chemotherapy based on Galsky (2011), must also meet the following criteria:
   i. UTUC should be Stage ≥pT2 pN0-2 (post-lymphadenectomy or no lymphadenectomy [pNx]), or pN+, M0.

ii. UBC should be Stage ≥pT3 or pN+, M0.

e. Must have a centrally reviewed negative postoperative computed tomography (CT) (defined as lymph nodes with short axis <1.0 cm and without growth and no distant metastases according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or negative biopsy within 28 days before randomization to confirm absence of disease at baseline.

5. If they have had AEs associated with prior surgery or neoadjuvant chemotherapy, they have stabilized or resolved to Grade ≤2 before randomization.
6. Have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2.
7. If a woman of childbearing potential, must have a negative pregnancy test within 7 days of the first dose of study drug. A woman is not of childbearing potential if she has undergone surgical sterilization (total hysterectomy, or bilateral tubal ligation, or bilateral oophorectomy ≥6 weeks before taking study drug) or if she is postmenopausal and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for ≥12 months, and there is no other cause of amenorrhea (eg, hormonal therapy, prior chemotherapy).

   Women of childbearing potential and males whose sexual partners are women of childbearing potential must agree to use barrier contraception and a second form of contraception (Clinical Trials Facilitation Group 2020) while receiving study drug and for 1 month following their last dose of study drug. Alternatively, total abstinence is also considered a highly effective contraception method when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. (Highly effective contraception methods are specified in the protocol.

   Sexually active males must use a condom during intercourse while taking study drug and for 1 month after the last dose of study drug and should not father a child during this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the study drug via seminal fluid.

   Study subjects must agree to refrain from donating sperm and eggs during the study and for 1 month following their last dose of study drug.
8. Are willing and able to comply with study visits and study procedures.

**Main exclusion criteria:**

1. Presence of positive invasive surgical margins following nephroureterectomy, distal ureterectomy, or cystectomy. In subjects not eligible for further surgery, radiotherapy, or other efficacious treatment, microscopic positive noninvasive margins (eg, carcinoma in situ) without gross residual disease are allowed.
2. Have received Bacillus Calmette-Guerin (BCG) or other intravesical therapy for nonmuscle invasive bladder cancer (NMIBC) within the previous 30 days.
3. Are currently receiving or are planning to receive during participation in this study, treatment with agents that are known moderate or strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone.
   Prior anticancer or other therapies are restricted as follows:
   a. Prior adjuvant treatment for urothelial cancer is not allowed.
   b. Prior neoadjuvant therapy (eg, chemotherapy, immunotherapy, or investigational) is allowed if inclusion criterion #4 is met.
      Prior neoadjuvant chemotherapy must have been completed within a period of time that is greater than the cycle length used for that treatment before first dose of study drug.

c. Prior biologic, immunotherapy, or investigational therapy should have been completed within a period that is ≥5 half-lives or 30 days, whichever is shorter, before the first dose of study drug.

4. Are planning to receive other systemic therapies intended to treat invasive urothelial carcinoma while on this study.
5. Have previously or currently is receiving treatment with a mitogen-activated protein kinase (MEK) or selective FGFR inhibitor.
6. Have a history of primary malignancy within the past 3 years other than (1) invasive UBC or UTUC (ie, disease under study), (2) noninvasive urothelial carcinoma, (3) any adequately treated in situ carcinoma or non-melanoma carcinoma of the skin, (4) any other curatively treated malignancy that is not expected to require treatment for recurrence during participation in the study, or (5) an untreated cancer on active surveillance that may not affect the subject's survival status for ≥3 years based on clinician assessment/statement and with medical monitor approval. For any other cancers that do not meet the criteria above, and for which the natural history or treatment do not have the potential to interfere with the safety or the efficacy assessments of the study, written approval is required by the medical monitor.
7. Have current evidence of corneal keratopathy or retinal disorder including, but not limited to, bullous/band keratopathy, inflammation or ulceration, keratoconjunctivitis, macular degeneration, or diabetic retinopathy, confirmed by ophthalmic examination. Subjects with asymptomatic ophthalmic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.
8. Have a history and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, vasculature, myocardium, and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, small renal cyst or stone calcifications, and asymptomatic coronary calcification.
9. Have impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
10. Have current evidence of endocrine alterations of calcium/phosphate homeostasis (eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis), unless well controlled.
11. Have consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, or Seville oranges or products containing juice of these fruits within 7 days before the first dose of study drug; have taken any Chinese herbal medicine or Chinese patent medicine treatments with anticancer activity within 14 days of the first dose of study drug.
12. Have insufficient bone marrow function:
    a. Absolute neutrophil count (ANC) <1,000/$mm^3$ ($1.0 \times 10^9$/L).
    b. Platelets <75,000/$mm^3$ ($<75 \times 10^9$/L).
    c. Hemoglobin <8.5 g/dL; transfusion support is allowed if >1 week before randomization and hemoglobin remains stable.
13. Have insufficient hepatic and renal function:
    a. Total bilirubin >1.5 × upper limit of normal (ULN) of the testing laboratory (for subjects with documented Gilbert syndrome, direct bilirubin must be ≤1.5 × ULN and enrollment requires approval by the medical monitor).
    b. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) >2.5 × ULN of the testing laboratory.

c. Serum creatinine >1.5 × ULN or a calculated (using the Cockcroft-Gault [C-G] formula [Cockcroft 1976]) or measured creatinine clearance of <30 mL/min.

14. Have amylase or lipase >2.0 × ULN.
15. Have abnormal calcium or phosphorus:
    a. Inorganic phosphorus higher than 1.02 × ULN of the testing laboratory.
    b. Total serum calcium (can be corrected) higher than 1.02 × ULN of the testing laboratory.
16. Have clinically significant cardiac disease including any of the following:
    a. New York Heart Association (NYHA) Class ≥2B; subjects with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the NYHA classification.
    b. Uncontrolled hypertension (refer to European Society of Cardiology and European Society of Hypertension guidelines [Williams 2018]).
    c. Presence of CTCAE v5.0 Grade ≥2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality.
    d. Unstable angina pectoris or acute myocardial infarction ≤3 months before the first dose of study drug.
    e. Average QT interval corrected by Fridericia's formula (QTcF) >470 msec (males and females). Note: If the QTcF is >470 msec in the first electrocardiogram (ECG), a total of 3 ECGs separated by ≥5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤470 msec, the subject meets eligibility in this regard.
    f. History of congenital long QT syndrome.
17. Have had a recent (≤3 months before the first dose of study drug) transient ischemic attack or stroke.
18. If female, are pregnant or nursing (lactating), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotrophin urine or blood laboratory test.
19. Have a known allergy/hypersensitivity reaction to any components of the study drug.
20. Have any other concurrent disease or condition that, in the view of the investigator, would interfere with study participation.

**Investigational product, dosage, and mode of administration:** Infigratinib 125 mg (administered orally as one 100-mg capsule and one 25-mg capsule) once a day using a "3-weeks on, 1-week off" schedule for each 28-day treatment cycle.

**Duration of treatment:** Treatment in each cohort was to be continued for a maximum of 52 weeks (13 cycles) or until local/regional or contralateral invasive or metastatic recurrence (whichever occurred first) was confirmed by BICR, or other prespecified criteria was met as per the protocol, whichever occurred first.

**Reference therapy, dosage, and mode of administration:** Placebo, supplied as hard gelatin capsules, matching the test article, administered orally, once a day using a "3-weeks on, 1-week off" schedule for each 28-day treatment cycle.

**Criteria for evaluation:**

This abbreviated clinical study report (CSR) represents the final formal analysis of Study QBGJ398-302. Due to early termination of the study by the sponsor, results will focus primarily on the primary and key secondary endpoints of the study.

**Statistical methods:**

**Efficacy:** The primary analyses for efficacy endpoints were based on the intent-to-treat (ITT) population, which included all subjects who were randomized. Subjects were analyzed by the treatment cohort randomized to, regardless of the treatment received.

The primary efficacy analysis endpoint was DFS as assessed by BICR, calculated as the number of months from randomization to local/regional invasive or metastatic recurrence ([date of DFS event - date of randomization + 1]/ [365.25/12]), or death due to any cause, whichever was earlier. Subjects without documented recurrence and still alive, were to be censored at the last complete disease assessment (or at the time of randomization, if no disease assessments were performed after the baseline visit or no death recorded).

The secondary variables included assessment of intraluminal low-risk recurrence as assessed by DFS, investigator assessed DFS, investigator assessed metastasis-free survival (MFS), and overall survival (OS).

The investigator-reviewed MFS was defined as the time from randomization to any metastatic recurrence as determined by the investigator, or death due to any cause, whichever occurred earlier. Subjects without documented metastatic recurrence and still alive were to be censored at the last radiology assessment, or at the time of randomization if no radiology disease assessments were performed after the baseline visit.

Overall survival time was defined as the number of months from randomization to death ([(date of death - date of randomization + 1]/[365.25/12]). Subjects who had not died (no record of death) or were lost to follow-up were censored at the date last known to be alive. Subjects who withdrew consent for study participation, including consent to be followed, were censored on the date of withdrawal.

Time to event endpoints (ie, DFS, MFS, and OS) were analyzed by Kaplan-Meier (K-M) method. Due to early termination of the study by the sponsor, no statistical tests were conducted.

With the limited number of subjects randomized at the time of the decision to terminate the study early, the number of DFS events required to assess the efficacy objectives was not achieved to the futility of the study. No formal inferential testing of efficacy was done.

**Safety:** Safety analyses were performed on the safety analysis population which included all subjects who were randomized and received at least one dose of study treatment. Subjects were analyzed by the treatment received.

The safety evaluation was based on tolerability of study treatment, AE reporting, laboratory parameters, pregnancy outcome (if applicable), ophthalmic assessments, 12-lead ECGs, vital signs, and ECOG performance status. Standard safety presentations were prepared, including summaries of AEs of special interest.

**RESULTS**

This abbreviated CSR represents the final formal analysis of Study QBGJ398-302 with focus on efficacy and safety results.

**Study Subjects:**

In total, 39 subjects were enrolled from North America (35.9%) and Western Europe (64.1%). Most subjects were white (84.6%) and male (84.6%). Median age of the study population was 70.0 years (range: 34, 88); 27 subjects (69.2%) were ≥65 years, and 25 subjects (64.1%) were <75 years. Twenty subjects were treated with infigratinib and 19 subjects received placebo.

All study subjects had an ECOG PS classification of 0 or 1, with the majority (66.7%) having a score of "0." Most subjects had UTUC (59.0%), with approximately equal proportions having urothelial (46.2%) and papillary urothelial (38.5%) histology, and the majority had Stage 3 tumors (59.0%). The median time from initial diagnosis to randomization was 182.0 days. Overall, 36 of 39 subjects had genetic alterations determined by the central laboratory, with the greatest proportion consisting of mutations (26 subjects [66.7%]). The overall tumor mutation burden was considered low (30 subjects [76.9%]).

Proportionately, subjects in the infigratinib cohort were more likely to have ECOG PS scores of "0" (75.0% vs. 57.9% for placebo), a shorter median time from initial diagnosis to randomization (146.5 days vs. 212.0 days for placebo), and a low tumor mutational burden (85.0% vs 68.4% for placebo).

**Efficacy Results:**

For the primary endpoint (DFS by BICR), data were censored for 85.0% to 89.5% of all subjects. Since the non-censored events never reached 50% of subjects, the K-M median is not applicable (NA). Three subjects in the infigratinib cohort had available data, with a median DFS of 5.3 months (range: 0.03, 17.48). For the 2 subjects in the placebo cohort with available data, median DFS was 5.4 months (range: 0.03, 20.90). K-M estimates for median DFS assessed by BICR was NA for both cohorts.

Results for the secondary endpoints were similar to the BICR assessment of efficacy, with data censored for most subjects. In terms of DFS assessed by the investigator, 7 subjects in the infigratinib cohort had available data with a median DFS of 6.4 months (range: 0.03, 18.07); the median K-M estimate was 11.3 months. For the 3 subjects in the placebo cohort with available data, median DFS was 12.2 months (range: 0.03, 21.36); the median K-M estimate was NA.

Median MFS for the 3 subjects in the infigratinib cohort with available data was 6.5 months (range: 0.03, 18.07); the median K-M estimate was NA (95% confidence interval (CI) for the median: 8.41, NA). For the 2 subjects in the placebo cohort with available data, median MFS was 12.2 months (range: 0.03, 21.36); the median K-M estimate was NA.

For OS, an event of death occurred in 3 subjects: 2 (10.0%) in the infigratinib cohort and 1 (5.3%) in the placebo cohort. The median OS was 13.1 months and 16.7 months, respectively.

**Safety Results:**

Overall, the safety profile observed in this study was consistent with the expected on-target effects of and AEs described for infigratinib as well as expected AEs for subjects with invasive urothelial carcinoma with susceptible FGFR3 genetic alterations.

- Exposure: Among subjects treated with infigratinib, median duration of exposure was 2.17 months (range: 0.0, 11.8). Fourteen subjects (70%) were exposed to infigratinib for ≤5 months, 2 (10%) were exposed between 7 and ≤11 months, and 4 (20%) were exposed for >11 months. Median relative dose intensity (RDI) was 80% (range: 49.5%, 100%). No infigratinib-treated subjects had an RDI >100%.
  Subjects treated with placebo were treated for substantially longer periods of time, with higher RDI. The median duration of exposure to placebo was 5-fold longer, at 10.81 months (range: 1.0, 11.8), with 2 subjects (10.5%) exposed between 7 and ≤11 months, and 10 subjects (52.6%) were

exposed for >11 months. Median RDI was 97.6% (range: 68.6%, 102.9%). Two placebo-treated subjects (10.5%) had RDI >100%.

- Among subjects treated with infigratinib, 17 subjects (85.0%) had their dose of study drug interrupted, 11 (55.0%) had their dose reduced, and 13 (65.0%) had their dose permanently discontinued.

- TEAEs: Overall, 35 subjects (89.7%) had at least 1 TEAE. The most frequently reported TEAEs by preferred term (PT) were diarrhoea (14 subjects [35.9%]), blood creatinine increased and hyperphosphataemia (12 subjects [30.8%] each); fatigue (9 subjects [23.1%]), and alopecia and dry mouth (8 subjects [20.5%] each).
  - In most instances, these commonly occurring TEAEs were more prevalent among subjects treated with infigratinib compared with those in the placebo cohort. In particular, the proportions of infigratinib-treated subjects were ≥20% higher than for the placebo cohort for diarrhoea, blood creatinine increased, hyperphosphataemia, alopecia, dry mouth, dysgeusia, and decreased appetite
  - Among subjects treated with infigratinib, TEAEs were reported for 19 subjects (95.0%), and nearly all of these subjects required concomitant medication or procedure or had their dose of study drug interrupted (17 subjects [85.0%] each). Subjects treated with infigratinib accounted for all TEAEs leading to dose reduction and all but one instance of a TEAE leading to dose discontinuation (8 subjects [40.0%] each). Two subjects (10.0%) had serious TEAEs, both considered to have treatment-related events, and 6 subjects (30.0%) had Grade 3 or 4 TEAEs, of which 4 (20.0%) were treatment-related TEAEs.
    Among subjects treated with placebo, TEAEs were reported for 16 subjects (84.2%) and related TEAEs were reported for 6 subjects (31.6%). Eleven (57.9%) placebo subjects had TEAEs requiring intervention with concomitant medication or procedure. Substantially fewer placebo-treated subjects had TEAEs requiring a change in dose of study drug (≤4 subjects). Three placebo subjects (15.8%) had Grade 3 or 4 TEAEs compared with 6 infigratinib subjects, and none of these were considered related. The 1 subject (5.3%) in the study who died due to a TEAE was treated with placebo.
  - Grade 3 or Grade 4 TEAEs: In the infigratinib cohort, 6 subjects (30.0%) had at least one Grade 3 or Grade 4 TEAE (combined), with 5 subjects (25.0%) having Grade 3 TEAEs and 1 subject (5.0%) having a Grade 4 event. Grade 3 TEAEs reported for 1 subject (5.0%) each included: chronic kidney disease, diarrhoea, hydronephrosis, keratitis, palmar-plantar erythrodysesthesia syndrome, paronychia, and uveitis. The Grade 4 TEAE of paronychia was reported for 1 subject.
    In the placebo cohort, 3 subjects (15.8%) had at least one Grade 3 or Grade 4 TEAE (combined), with 2 subjects having Grade 3 events of ECG QT prolongation, lipase increased, and urinary tract obstruction and 1 subject having a Grade 4 event of urosepsis that deteriorated to Grade 5.

- Related TEAEs: In the infigratinib cohort, 19 subjects (95.0%) had treatment-related TEAEs, the most common of which were diarrhoea and hyperphosphataemia (each reported by 11 subjects [55.0%]); alopecia (8 subjects [40.0%]); blood creatinine increased (7 subjects [35.0%]); fatigue and dysgeusia (each reported by 5 subjects [25.0%]); and mucosal inflammation, dry mouth, and decreased appetite (each reported by 4 subjects [20.0%]).
  In the placebo cohort, 6 (31.6%) subjects had treatment-related TEAEs, the most common of which was mucosal inflammation (2 subjects [10.5%]).
  - Grade 3 or Grade 4 related TEAEs: Four infigratinib subjects (20.0%) had at least 1 treatment-related Grade 3 or 4 TEAE, with diarrhoea, keratitis, palmar-plantar

erythrodysaesthesia syndrome, and paronychia each reported by 1 subject (5.0%). No subjects in the placebo cohort had Grade 3 or 4 TEAEs assessed as related to study treatment.

- Subgroups: When TEAEs were reported by age (<65 years vs ≥65 years), overall a higher proportion of subjects in the older cohort reported TEAEs (25 subjects [92.6%]) compared to the <65 year cohort (10 subjects [83.3%]), though notably there more than were twice as many subjects in the older cohort. Of the most commonly reported TEAEs overall, a higher proportion of subjects in the younger cohort reported the TEAEs of hyperphosphataemia (41.7% for <65 years vs 25.8% for ≥65 years), alopecia (25.0% vs 18.5%), lipase increased (16.7% vs 11.1%), mucosal inflammation (16.7% vs 14.8%), and dry skin (8.3% vs 7.4%).
- Deaths: Three study subjects died. During the on-treatment period, Subject 302-194-029 in the placebo cohort died of urosepsis on Day 58. The TEAE was assessed as not related to study drug. During the posttreatment period, 2 subjects in the infigratinib cohort died due to underlying disease. Specifically, Subject 302-176-004 died on Day 172 due to underlying disease, and Subject 302-197-009 died on Day 460 of lymphogenous metastatic muscle-invasive urothelial carcinoma and deterioration of the underlying disease.
- SAEs: In total, 4 subjects experienced 8 SAEs, and 4 of these SAEs were treatment related. The single most commonly reported SAE was diarrhoea (2 subjects [5.1%]).
- Dose Changes due to TEAEs:
  - Nine subjects (23.1%) each had 1 TEAE that led to treatment discontinuation (8 [40.0%] infigratinib, 1 [5.3%] placebo). The only TEAE that led to treatment discontinuation in >1 subject was blood creatinine increased.
  - Twenty-one subjects (53.8%) had at least 1 TEAE that led to dose interruption (17 [85.0%] infigratinib, 4 [21.1%] placebo). The TEAEs that led to dose interruption in ≥10% of all subjects were blood creatinine increased (5 [25.0%] infigratinib, 1 [5.3%] placebo) and diarrhoea (4 [20.0%] infigratinib, 0 placebo).
  - Eight subjects (20.5%) had at least 1 TEAE that led to dose reduction (8 [40.0% infigratinib, 0 placebo), but none of these events were Grade 3 or higher, and none were SAEs. The TEAEs that led to dose reduction in >5% of subjects were blood creatinine increased and diarrhoea (5.1% each), all for subjects in the infigratinib cohort.
- Hyperphosphataemia was one of the most frequently reported TEAEs (12 subjects) and treatment-related TEAEs (11 subjects). This TEAE was only reported for subjects in the infigratinib cohort. Based on review of laboratory values, 18 subjects had elevated phosphate values postbaseline (16 infigratinib [80.0%] and 2 placebo [10.5%]).
- Assessment of AEs and laboratory measurements demonstrated little evidence of hepatic toxicity with infigratinib. Overall, 3 subjects (7.7%) had at least 1 occurrence of AST or ALT >3×ULN. Of these, 1 subject had an occurrence of ALT >5×ULN, as well as reports of both AST and ALT>3×ULN, and elevated alkaline phosphatase (ALP). There were no occurrences of AST or ALT >10×ULN, no occurrences of total bilirubin (TBL) ≥2×ULN, and no reports of elevated aminotransferase and total bilirubin on the same day or while on treatment.
- Overall, no clinically significant changes in visual acuity score or intraocular pressure (IOP) were noted for subjects in either treatment cohort.
- No clinically significant changes from baseline in left ventricular ejection fraction (LVEF), QTcF, or QTcB were detected for any subject.

**CONCLUSIONS**

On 05 October 2022, Helsinn Healthcare SA (HCC) made a business decision to discontinue development and commercialization of TRUSELTIQ™ (infigratinib). As a result of this decision, new drug and marketing authorization applications worldwide were withdrawn and the further development of infigratinib in oncology outside of China was terminated. This event subsequently led to the closure of this study. The decision to stop development of infigratinib in the oncology setting was not made based on any efficacy or safety concerns. At the time of the decision to terminate the study early, only 39 subjects were enrolled, which rendered the study futile. Consequently, no statistical testing could be done.

For the primary and secondary efficacy endpoint of MFS (per investigator), data were censored for 85.0% to 89.5% of all subjects, which resulted in K-M median values being NA. Three subjects in the infigratinib cohort had available data, with a median DFS of 5.3 months (range: 0.03, 17.48). For the 2 subjects in the placebo cohort with available data, median DFS was 5.4 months (range: 0.03, 20.90). K-M estimates for median DFS assessed by BICR was NA for both cohorts. Results for the secondary endpoints were similar to the BICR due to censoring of most subjects. The median OS was 13.1 months and 16.7 months, respectively.

Overall, the safety profile observed in this study was consistent with the expected on-target effects of and AEs described for infigratinib as well as expected AEs for subjects with invasive urothelial carcinoma. A higher proportion of subjects treated with infigratinib reported TEAEs, TEAEs requiring a change in dose and/or intervention with concomitant treatment, and treatment-related TEAEs. It is notable that hyperphosphataemia was one of the most frequently reported TEAEs (12 subjects) and treatment-related TEAEs (11 subjects), and it was only reported for subjects in the infigratinib cohort.

**Date of Report:** 02 August 2023