1. Protocol Summary

1.1. Synopsis

A Phase 2A/B, Multicenter, Open-Label Study Evaluating the Efficacy and Safety of dabogratinib (TYRA-300) in Participants with Low Grade Upper Tract Urothelial Carcinoma (SURF303)

Brief Title: A study to investigate dabogratinib (TYRA-300) in participants with LG UTUC

Rationale: Dabogratinib, also known as TYRA-300, is a highly selective inhibitor of fibroblast growth factor receptor 3 (FGFR3). The family of FGFR signaling plays a crucial role in tumorigenesis and progression of disease. Over recent years, several pan-FGFR inhibitors have received regulatory approvals for cancers such as locally advanced and metastatic bladder cancer (Balversa (erdafitinib)) and cholangiocarcinoma (Pemazyre (pemigatinib)), Truseltiq (infigratinib) and Lytogobi (futibatinib)). Additionally, each compound has explored development in cancers with high expression of FGFR 1-3 alterations. Each compound inhibits FGFR 1-4 to some degree; as a result, there are adverse events and tolerability issues that impact dosing. Dabogratinib is manufactured specifically to target FGFR3 with significantly diminished impact to receptors 1, 2 and 4. As a result, dabogratinib's safety profile demonstrates considerable improvement from the pan-FGFR inhibitors.

Upper tract urothelial carcinoma (UTUC) is a rare cancer of the urinary tract and accounts for approximately 5-10% of all urothelial carcinomas (Rouprêt, 2018), with the population being comprised of more elderly males (Ma, 2024). Approximately 30% of UTUC patients have low grade (LG) disease. Standard of care for UTUC includes ureteroscopic management, intracavitary chemotherapy, and nephroureterectomy. Administration of chemotherapy proves to be challenging due to the location of the lesions so percutaneous or retrograde approaches are most widely used. Unfortunately, the recurrence rate is high (35-75%) (Cutress, 2012, Lonergan, 2020; Raman, 2020) so nephroureterectomy is the default for curative treatment.

The incidence of FGFR3 alterations in LG UTUC patients across multiple studies have demonstrated FGFR3 mutations in over 80%, and in some cohorts up to 96%, of low-grade UTUC cases (Sfakianos, 2015; Moss, 2017; Nassar, 2019). With such a high prevalence of FGFR3 alterations in a population where the treatment options are challenging or life changing, introducing an oral, systemic therapy like dabogratinib may provide a viable treatment option for LG UTUC patients.

Objectives and Endpoints (Phase 2A):

Objectives	Endpoints
Primary	
To evaluate the efficacy of dabogratinib in participants with LG UTUC with FGFR3 altered tumors	Complete response (CR) rate within 6 months* in participants with LG UTUC with FGFR3 altered tumors. CR is determined by negative ureteroscopic examination, negative cytology and negative for-cause imaging and biopsy.
To select the recommended dose for Phase 2B	Determination of the recommended dose for Phase 2B based on integrated safety, PK, and efficacy data
Secondary	
To evaluate the efficacy of dabogratinib in all participants with LG UTUC	CR rate within 6 months* for all participants, regardless of FGFR3 alteration status in tumors
To evaluate the therapeutic activity of dabogratinib	• Duration of response (DOR) in participants with LG UTUC with FGFR3 altered tumors. • DOR in all participants regardless of FGFR3 alteration status in tumors. • CR rate at 12 months and 24 months in participants with LG UTUC with FGFR3 altered tumors. • CR rate at 12 months and 24 months in all participants regardless of FGFR3 alterations status in tumors. • Response rate within 6 months in participants with LG UTUC with FGFR3 altered tumors. • Response rate within 6 months in all participants regardless of FGFR3 alteration status in tumors.

Objectives	Endpoints
To evaluate the safety and tolerability of dabogratinib	Incidence and severity of adverse events (AEs), incidence of impact on study drug dosing, changes in clinical laboratory parameters, vital sign changes
To characterize the PK profile of dabogratinib	PK parameters may include C_{max}, T_{max}, $AUC_{0\text{-last}}$, AUC_{Tau}, $AUC_{0\text{-}\infty}$ (after first dose only), Vd/F, CL/F, and $t_{1/2}$.
To determine rate of renal preservation after treatment with dabogratinib	Proportion of participants who did not undergo nephrectomy or nephroureterectomy
To evaluate the change from unresectable to resectable disease after treatment with dabogratinib	Proportion of participants with unresectable disease at baseline who convert to resectable disease or CR on dabogratinib, as assessed by the Investigator
Exploratory	
To evaluate markers of FGFR engagement/inhibition, tumor response and resistance in blood, tissue and urine	Assessment of pharmacodynamic markers (serum phosphorous, proteomic analysis, FGF19, KLB and 7α-hydroxy-4-cholesten-3-one), tumor response, utDNA, comprehensive genomic profiling and changes in transcriptional activation of FGF/FGFR-associated genes
To compare tissue-based and urine tumor DNA (utDNA)-based genomic testing	Concordance rate of baseline utDNA clinical trials assay (CTA), tissue-based NGS testing of archival tissue samples and/or prior local NGS results
To assess excretion of dabogratinib into the urine	Measure the amount of intact dabogratinib excreted in the urine
To assess patient reported outcomes (PRO) for systemic treatment of LG UTUC	EORTC QLQ C30 questionnaire results measuring the impact on quality of life using systemic therapy
To evaluate the long-term benefit of dabogratinib in all participants	Progression-free survival

Objectives	Endpoints
To assess the role of dabogratinib in facilitating endoscopic management	Assessment of change in Upper TRACT Endometry Score in participants after treatment with dabogratinib

*Participants with reduction in marker lesion(s) at 3 months as per Investigator assessment, but still have evidence of disease, may continue to receive treatment and be re-assessed for CR at 6 months.

Objectives and Endpoints (Phase 2B)

Objectives	Endpoints
Primary	
To evaluate the efficacy of dabogratinib in participants with LG UTUC with FGFR3 altered tumors.	Complete response (CR) rate within 6 months* in participants with LG UTUC with FGFR3 altered tumors. CR is determined by negative ureteroscopic examination, negative cytology and negative for-cause imaging and biopsy.
Secondary	
To evaluate the efficacy of dabogratinib in all participants with LG UTUC	CR rate within 6 months* for all participants, regardless of FGFR3 alteration status in tumors
To evaluate the therapeutic activity of dabogratinib	• Duration of response (DOR) in participants with LG UTUC with FGFR3 altered tumors. • DOR in all participants regardless of FGFR3 alteration status in tumors. • CR rate at 12 and 24 months in participants with LG UTUC with FGFR3 altered tumors. • CR rate at 12 and 24 months in all participants regardless of FGFR3 alterations status in tumors. • Response rate within 6 months in participants with LG UTUC with FGFR3 altered tumors. • Response rate within 6 months in all participants regardless of FGFR3 alteration status in tumors.
To evaluate the safety and tolerability of dabogratinib	Incidence and severity of AEs, incidence of impact on study drug dosing, changes in clinical laboratory parameters, vital sign changes

Objectives	Endpoints
To determine rate of renal preservation after treatment with dabogratinib	Proportion of participants who did not undergo a nephrectomy or nephroureterectomy
To evaluate the change from unresectable to resectable disease after treatment with dabogratinib	Proportion of participants with unresectable disease at baseline who convert to resectable disease on dabogratinib, as assessed by the Investigator
To characterize the PK profile of dabogratinib	PK parameters may include C_{max}, T_{max}, $AUC_{0\text{-last}}$, AUC_{Tau}, $AUC_{0\text{-}\infty}$ (after first dose only), Vd/F, CL/F, and $t_{1/2}$
Exploratory	
To assess PRO for systemic treatment of LG UTUC	EORTC QLQ C30 questionnaire results measuring the impact on quality of life using systemic therapy
To evaluate the long-term benefit of dabogratinib in all participants	Progression-free survival
To assess the role of dabogratinib in facilitating endoscopic management	Assessment of change in Upper TRACT Endometry Score in participants after treatment with dabogratinib

*Participants with reduction in marker lesion(s) at 3 months as per Investigator assessment, but still have evidence of disease, may continue to receive treatment and be re-assessed for CR at 6 months.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Below are the inclusion and exclusion criteria for both Phase 2A and Phase 2B participants.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participants ≥ 18 years of age at the time of informed consent and willing and able to comply with all required study procedures.
2. Confirmed LG UTUC (both favorable and unfavorable sub-stratification as per AUA Clinical Risk Stratification are eligible).
    a. At least 1 measurable papillary LG tumor, as per Investigator assessment at time of URS. Tumors may be located in renal pelvis, infundibula/infundibulum, calyces and/or ureter.
    b. Biopsy taken from at least 1 tumor showing LG UTUC; the most suspicious lesion should be biopsied, if safe and feasible. Participants who have been biopsied within 8 weeks before Screening for this study and shown to have LG UTUC may have these historical biopsies used for enrollment into the study and do not require repeat biopsy during Screening. The most recent biopsy is the qualifier for enrollment.
3. Participants should have at least 1 remaining papillary LG tumor evaluated visually with a diameter of at least 5 mm or multiple lesions with an aggregate size of at least 5 mm (there is no minimum size for individual lesions) post-biopsy; marker lesion(s) should not be lesions that have been biopsied or partially resected, if possible. In the case of a solitary lesion, the lesion should be biopsied for histological assessment and left in place as a marker lesion.
    a. Participants with bilateral LG UTUC may be enrolled as long as both sides qualify for all inclusion and exclusion criteria. Both sides will require biopsy and marker lesions. Note: If both upper tracts meet inclusion criteria, the treating urologist should consult with the Sponsor to discuss evaluation measures.
    b. Participants with hydronephrosis caused by an obstruction are eligible to participate, however the obstruction should be relieved through resection or stenting during the pre-Screening ureteroscopy.
4. Participants must have archival/fresh tissue in the form of around 10 unstained slides or FFPE with at least 20% tumor in addition to urine sample for retrospective genomic testing using the Sponsor's genomic assay; this includes participants who have been previously tested and have a genomics report on file. In participants with unresectable disease or tissue that cannot be collected for other reasons, upper tract washing is acceptable (refer to Section 8.1.1 for details). NOTE: FGFR results are not required for enrollment.

5. Identification of marker lesion(s) within 8 weeks prior to randomization (refer to Inclusion Criterion #2)
6. If synchronous NMIBC, NMIBC must be fully resected and low-grade Ta or T1
7. No prior BCG administration within 1 year of date of consent.
8. No intravesical chemotherapy within 8 weeks prior to C1D1 (including UGN-101).
9. No systemic chemotherapy within 3 months prior to C1D1
10. ECOG 0-2
11. Pathology consists of pure urothelial carcinoma
12. Adequate bone marrow, liver, and renal function:
    a. Bone marrow function:
        i. Absolute neutrophil count (ANC) ≥1,500/mm3
        ii. Platelet count ≥75,000/mm3
        iii. Hemoglobin ≥10.0 g/dL
    b. Liver function:
        i. Total bilirubin ≤ ULN
        ii. Alanine aminotransferase (ALT) ≤ ULN
        iii. Aspartate aminotransferase (AST) ≤ ULN
    c. Renal function:
        i. Estimated glomerular filtration rate >60 mL/min calculated using the modification of diet in renal disease equation or CKD-EPI formula
    d. Serum Phosphate level ≤ ULN prior to starting treatment
    e. Coagulation
        i. International normalized ratio (INR) ≤1.5 × ULN
13. Ability to swallow tablets
14. Participants (male and female) of child-bearing potential (including females who are post-menopausal for less than 1 year) and their partners must be willing to practice effective contraception while on treatment and be willing and able to continue contraception for 3 months (males) and 6 months (females) after the last dose of study treatment. Potential male participants should consider the potential impact of dabogratinib on their ability to father a child and discuss options with the site study staff. The participants must also refrain from donating sperm during this period. Please refer to Appendix 2 for more details.
15. Potential participants who are diagnosed with human immunodeficiency virus (HIV) must have a viral load below the limits of detection and must be on stable doses of antiretroviral therapy for at least 3 months prior to C1D1. **NOTE**: some of the compounds in antiretroviral therapy may be on the prohibited medications list. Allowance will be made to ensure the

participant's HIV treatment continues uninterrupted following a discussion with the Sponsor's medical monitor. A discussion of the impact of the antiretroviral therapy on dabogratinib needs to be discussed with the potential participant prior to C1D1.

16. Potential participants with chronic hepatitis B virus infection with active disease should be on a suppressive antiviral therapy prior to C1D1.
17. Potential participants with a history of hepatitis C virus (HCV) infection should have completed curative antiviral treatment and must have an HCV viral load below the limit of quantification.
18. Potential participants with a history of HCV infection and on current treatment must have an HCV viral load below the limit of quantification

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Evidence of or any features of HG UTUC
2. History of carcinoma in situ (CIS)
3. History of prostatic urethral involvement
4. Current or previous history of muscle invasive bladder cancer
5. Current or previous history of lymph node positive and/or metastatic bladder cancer
6. Evidence of squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma or small cell of the bladder
7. Currently receiving systemic cancer therapy (cytotoxic or immunotherapy)
8. Current or prior history of pelvic external beam radiotherapy for bladder cancer
9. Current or history of receiving a prior FGFR inhibitor
10. Systemic immunotherapy within 6 months prior to randomization
11. Treatment with an investigational agent within 30 days or 5 half-lives from randomization, whichever is shorter; compounds with an unknown half-life will be default to 30 days.
12. Prior treatment with an intravesical or intracavitary agent within 8 weeks of C1D1
13. Requiring use of medications that are potential inhibitors or inducers of CYP3A (prohibited list of medications)
14. Had major surgery within 4 weeks prior to C1D1
15. Any reason that in the view of the Investigator, would substantially impair the ability of the participant to comply with study procedures and/or risk to the participant (i.e., uncontrolled diabetes)
16. Females who are pregnant, breastfeeding or planning to become pregnant within 6 months after the last dose of dabogratinib and males who plan to father a child while enrolled in this study or within 3 months after the last dose of dabogratinib
17. Has impaired wound healing capacity
18. Any ocular condition likely to increase the risk of eye toxicity
19. Current evidence of central serous retinopathy or retinal pigmented epithelial detachment of any grade at time of baseline examination.
20. History of or current uncontrolled cardiovascular disease

21. Gastrointestinal disorders that will affect oral administration or absorption of dabogratinib
22. Uncontrolled HIV infection, or uncontrolled hepatitis B or C
23. History of a second primary malignancy within 3 years of signing ICF, except for skin cancers that have been resected with clear margins and other malignancies that have been cured and are under active-surveillance (i.e., prostate, breast).
24. Known allergy to dabogratinib or any excipients of the formulated product
25. History of prolonged QT syndrome or baseline heart rate-corrected QT interval using Fridericia formula (QTcF) interval >470 ms

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 2 weeks before the start of study intervention until 1 week after the final dose.

5.4. Screen Failures

A screen failure occurs when a participant who has signed the main consent to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE related to study procedures.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should re-sign the informed consent and be assigned a new participant number.