1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Multicenter, Open-Label Study Evaluating the Efficacy and Safety of TYRA-300 in FGFR3 Altered Low Grade, Intermediate Risk Non-Muscle Invasive Bladder Cancer (SURF302)

Brief Title: Phase 2 Study of TYRA-300 in FGFR3 Altered Low Grade, Intermediate Risk NMIBC

Rationale:

Dabogratinib (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 cancer. 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 Lytgobi [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 designed specifically to target FGFR3 with significantly lower potency to receptors 1, 2 and 4. As a result, dabogratinib has the potential to demonstrate a different safety profile from pan-FGFR inhibitors.

Non-muscle invasive bladder cancer (NMIBC) has a high degree of activating FGFR3 mutation and fusions. Up to 80% (Haas 2025) of NMIBC cases have shown activating FGFR3 mutations or fusions present. However, as bladder cancer becomes more aggressive and more progressive (muscle invasive, locally advanced, metastatic), the number of activating FGFR3 mutations and fusions decreases. Metastatic bladder cancer has up to 20% of activating FGFR3+ alterations (Ascione 2023).

This study will investigate the safety and tolerability, efficacy, PK, and PD of dabogratinib and assess different doses of dabogratinib in participants harboring FGFR3 mutations and/or fusions with intermediate risk NMIBC in order to identify the Phase 3 dose. Starting from the 10th participant, Bayesian futility monitoring will be applied using the efficacy stopping boundaries described in Section 9.3.

Key Objectives and Endpoints:

Key Objectives	Key Endpoints
Primary	
To assess the efficacy of dabogratinib in low grade (LG) intermediate risk (IR)-NMIBC participants	• Complete response (CR) rate at 3 months, defined as the proportion of participants with negative cystoscopy, negative cytology, and negative directed biopsy, if required.
Secondary	
To further evaluate the efficacy of dabogratinib	• Duration of response (responders only), defined as the time from initial response to confirmed recurrence of disease or death from any cause, whichever occurs first. • Time to recurrence (responders only), defined as the time from start of response to confirmed recurrence of disease • Recurrence-free survival rate (responders only) at 12 months and 24 months
To evaluate the safety and tolerability of dabogratinib	• Incidence and severity of adverse events according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 5.0, incidence of impact on Study Drug dosing, changes in clinical laboratory parameters, vital sign changes

Overall Design:

This is an open-label, randomized, Phase 2, multi-center study to determine the safety and tolerability, efficacy, and recommended dose for Phase 3 of dabogratinib in participants with low-grade intermediate risk NMIBC that harbor FGFR3 mutations and/or fusions.

Up to approximately 240 evaluable participants may be enrolled (up to 30 participants per dose cohort in up to 3 dose cohorts and up to approximately 150 participants in the Expansion Cohort at the selected dose). Note: An enrolled participant is defined as one who provides informed consent (or assent, if applicable), meets all eligibility criteria, and who is subsequently randomized (when applicable) or receives their first dose (for non-randomized participants). This study will utilize a safety review committee (SRC) to continuously monitor the ongoing safety of participants as well as recommend the dose and appropriateness of opening additional cohorts (further described in Section 4.1.1 and detailed in the SRC Charter).

Initially participants will be randomized to 1 of 2 doses of dabogratinib as follows:

- Dose Cohort A (DCA): 60 mg once daily (QD)
- Dose Cohort B (DCB): 50 mg (QD)

Note: Justification for the doses and regimen are provided in Section 4.2.

A third dose (Dose Cohort C (DCC)) may be evaluated based on the SRC and Sponsor's review of all available safety, preliminary efficacy, PK, and PD data from DCA and DCB. Starting from the 10th participant, Bayesian futility monitoring will be applied using the efficacy stopping boundaries described in Table 13. Refer to Section 9.3 for additional details. In the event DCC is opened for enrollment and either DCA or DCB is closed, enrollment will prioritize DCC, with participants backfilled into DCC until enrollment is balanced with the remaining open dose level (DCA or DCB). Once enrollment is balanced across open dose level cohorts, randomization can resume at a 1:1 ratio. If both DCA and DCB are closed due to emerging data, DCC may be enrolled alone.

After approximately 50 participants have been enrolled in DCA and DCB or approximately 75 participants enrolled if DCC is opened, the SRC will convene to review the totality of available safety, preliminary efficacy, PK, and PD data. After reviewing the data, the SRC will provide a recommendation to the Sponsor whether to open the Expansion Cohort or not (upon completion of enrollment of dose finding cohorts) and the dose of dabogratinib to administer. The Expansion Cohort will enroll participants with LG IR NMIBC ± focal HG disease and no upper limit on marker lesion tumor volume (further described in Sections 2 and 5.1). Initially, the Expansion Cohort will enroll 70 participants with the potential to expand up to 150 (sample size justification provided in Section 9.3) at the Sponsor's discretion.

All participants will receive dabogratinib orally QD for each 28-day cycle. Dabogratinib administration instructions are provided in Section 6.1. Participants will continue to receive treatment for up to 24 months or until disease recurrence (defined as disease recurrence in the bladder, progressive disease in or out of the bladder, or development of extravesical disease), toxicity, lost to follow-up, or the Sponsor closes the study, whichever occurs first. Overall, the anticipated study duration for an individual participant is 36 months.

Study Population:

Key Inclusion Criteria

1. Participants age ≥ 18 at the time of informed consent and willing and able to comply with all required study procedures
2. Able to understand and give written informed consent
3. **DCA, DCB, and DCC only:** Participants with histologically confirmed low grade NMIBC within 8 weeks prior to C1D1 with prior diagnostic biopsy/TURBT to confirm stage and grade and with at least 3 mm and not more than 12 mm total residual (1/2 a resectoscope loop to 2 loops, refer to Section 8.1.6) visible tumor as a marker lesion(s) left behind:
    a. Ta low grade
    b. T1 low grade

4. **Expansion Cohort Only:** Participants with histologically confirmed low-grade NMIBC within 8 weeks prior to enrollment with prior diagnostic biopsy/TURBT to confirm stage and grade and with at least 3 mm (1/2 a resectoscope loop, refer to Section 8.1.6) residual visible tumor as a marker lesion(s) left behind (**Note**: There is no upper limit on tumor size):
    a. Ta low grade ± Focal high-grade
    b. T1 low grade
5. Documented negative voided urine cytology within 2 weeks of C1D1
6. Participants must have intermediate risk NMIBC, defined as having any of the following characteristics (AUA Guidelines, 2024)
    a. Recurrence within 1 year, LG Ta
    b. Solitary LG Ta >3cm
    c. LG Ta, multifocal
    d. LG T1
7. Documented activating FGFR3 alteration (mutation or fusion) in a CLIA-certified or equivalent laboratory (Appendix 3)
8. Have undergone bladder mapping and identification of marker lesion(s) within 8 weeks prior to C1D1 (refer to Inclusion Criterion #2 & #3)
9. No evidence of urothelial carcinoma of the upper urinary tract (confirmed by imaging) or prostatic urethra within 6 months of C1D1
10. No prior Bacillus Calmette-Guérin (BCG) administration within 3 months of date of consent.
11. No intravesical chemotherapy within 8 weeks prior to C1D1.
12. ECOG 0-1
13. Pathology consistent with pure urothelial carcinoma; if mixed histology, ensure that at least 80% of the sample is urothelial
14. 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
   ii. Serum phosphate level ≤ ULN prior to starting treatment
d. Coagulation
   i. International normalized ratio (INR) ≤1.5 × ULN

Key Exclusion Criteria

1. Current or previous history of muscle invasive bladder cancer
2. Current or previous history of lymph node positive and/or metastatic bladder cancer
3. Evidence of pure squamous cell carcinoma, pure adenocarcinoma or pure undifferentiated carcinoma of the bladder
4. Currently receiving systemic cancer therapy (cytotoxic or immunotherapy)
5. Current or prior history of pelvic external beam radiotherapy for bladder cancer
6. Current or history of receiving a prior FGFR inhibitor
7. Systemic immunotherapy for the treatment of cancer within 6 months prior to C1D1
8. Treatment with an investigational agent within 30 days or 5 half-lives from C1D1, whichever is shorter; compounds with an unknown half-life will be default to 30 days.
9. Prior treatment with an intravesical agent within 8 weeks of C1D1,
10. Current evidence of central serous retinopathy (CSR) or retinal pigmented epithelial detachment (RPED) of any grade at time of baseline examination as well as any active ocular abnormality at baseline that may increase the chance for ocular toxicity.