

HEAT BIOLOGICS, INC.

STATISTICAL ANALYSIS PLAN FOR PROTOCOL HS410-101

A Phase 1/2, Placebo-Controlled, Randomized Study to Evaluate the Safety, Immune Response and Clinical Activity of HS-410 in Patients with Non-Muscle Invasive Bladder Cancer Who Have Undergone Transurethral Resection of Bladder Tumor (TURBT)

Protocol number: HS410-101
Study phase: Phase 1/2
Product name: Vesigenurtacel-L (HS-410)
Indication: Non-muscle invasive bladder cancer
Investigators: Multicenter
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Confidential Statement

Information in this document is confidential and should not be disclosed, other than to those directly involved in the execution of the study, without written authorization from the sponsor.

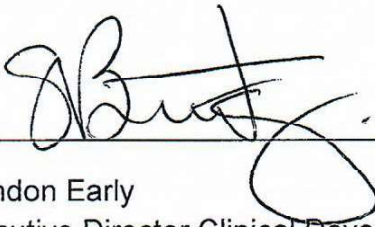
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List of Abbreviations

AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
BCG	Bacillus Calmette–Guérin
CBC	Complete blood count
CI	Confidence interval
CIS	Carcinoma in situ
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
CTLA4	Cytotoxic T-lymphocyte associated antigen 4
DFS	Disease free survival
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gzB	Granzyme B
HR	Hazard Ratio
HLA	Human leukocyte antigen
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
IHC	Immunohistochemistry
IBC	Institutional biosafety committee
ICS	Intracellular cytokine staining
IHC	Immunohistochemistry
IR	Immunologic Response
IRB	Institutional Review Board
ISR	Injection Site Reaction
ITT	Intention to treat
i.v.	Intravenous
IXRS	Interactive Response System
LTFU	Long-term Follow-up
MedRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
95%CI	95% confidence interval
OR	Odds ratio
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell

PCR	Polymerase Chain Reaction
PD	Progressive Disease
RBC	Red blood cell
RECIST	Response evaluation criteria for solid tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation OR Stable Disease
SAR	Suspected adverse reaction
SOA	Schedule of Assessments
SOE	Schedule of events
SOC	Standard of care
TCR	T-cell receptor
TURBT	Transurethral resection of bladder tumor
ULN	Upper limits of normal
TCR	T-cell Receptor
TEAE	Treatment emergent adverse event
TIL	Tumor Infiltrating Lymphocyte
TKI	Tyrosine Kinase Inhibitor
ULN	Upper limit of normal
US	United States
WBC	White blood cell

1. Introduction

1.1 Preface

Bladder cancer is the 6th most common cancer in the United States with an estimated 74,690 patients diagnosed in 2014 and 15,580 deaths.¹ Approximately 70-80% of patients have non-muscle invasive bladder cancer (NMIBC) at the time of diagnosis.^{2,3} Transurethral resection of bladder tumour (TURBT) is the standard treatment for NMIBC and aids in the proper diagnosis and staging of disease. Patients with low-risk disease (solitary, primary low-grade, Ta tumours) have high recurrence-free and progression-free rates and an overall favorable prognosis.⁴ In contrast, patients with high-risk disease (T1 and/or high grade and/or *carcinoma in situ (CIS)*) determined at the time of initial resection have a one year recurrence-free rate of approximately 39%.³

Between these two extremes are a large group of patients classified as having intermediate-risk disease, which is defined as multiple or recurrent low-grade Ta tumors.⁴ Since this is a very broad spectrum of patients, the intermediate-risk category can be further stratified. Intermediate-risk patients with at least 3 of the following 4 risk factors – multiple tumours, tumour size > 3cm, early recurrence (<1 year from previous TURBT), or frequent recurrences (i.e. recurrence with a frequency of more than once in any 12-month period) – have treatment regimens and outcomes similar to high-risk patients, with recurrence-free rates of 62% at 1 year and 38% at 5 years resectively.^{3,5} Patients with either high or intermediate-risk disease with 3 or more risk factors will make up the patient population for this protocol.

Adjuvant treatment options for patients with urinary bladder cancer are limited, as systemic chemotherapy appears largely ineffective in this setting.^{6,7} Adjuvant intravesical mitomycin-C and bacillus Calmette-Guérin (BCG) have been used successfully to reduce local recurrence of NMIBC for over 30 years, but nearly a quarter of high-risk patients have evidence of disease 6 months after induction BCG.⁸ Patients with intermediate- or high-risk disease benefit most when induction BCG is combined with a maintenance phase lasting for at least 1 year.^{9,10} However, nearly 15% of these patients will still go on to experience a recurrence after 3 years.¹⁰ Reasons for failure are not well defined, but may be related to toxicities associated with these agents resulting in utilization of intravesical therapy well below recommended dose intensities.^{11,12}

Given the limited long term disease control possible with currently available adjuvant strategies in patients with high risk NMIBC and the progressively less effective and more debilitating outcomes of subsequent rounds of surgical resection, there is a pressing need for alternate or complementary adjuvant strategies, such as vaccine-based immunotherapy, to reduce recurrence and improve tolerability of treatments in this patient group. Immunotherapy with vaccines and checkpoint inhibitors has demonstrated clinical benefit and a survival prolongation in several stage solid tumours such as prostate cancer and metastatic melanoma.^{13,14}

Vesigenurtacel-L is an allogeneic cellular immunotherapy designed to induce cell-mediated immunity and intended for use in treatment of non-muscle invasive bladder cancer (NMIBC). The active ingredient in vesigenurtacel-L is an engineered cell line derived from a human urothelial cancer cell line, UM-UC3, and has been modified to express a secreted gp96-Ig fusion protein. The secreted gp96 acts as a chaperone and adjuvant to induce cellular immune responses to various tumor antigens

expressed by the host cell. The expression plasmid encoding the gp96-Ig fusion protein lacks any sequences known to be capable of mediating integration into mammalian genomes.

After the expansion of cells using current good manufacturing practices (cGMP) the cells are irradiated to render them replication incompetent while maintaining biological activity, including the expression of secreted gp96 and associated tumor antigens.

1.2 Purpose of the analyses

These analyses will assess the efficacy and safety of HS-410 as monotherapy and in combination with BCG in patients with non-muscle invasive bladder cancer who have undergone TURBT.

2 Study Objectives and Endpoints

2.1 Study Objectives

Primary Objective

- **Phase 1:** To characterize the safety and tolerability of monotherapy vaccination with HS-410 in patients with non-muscle invasive bladder cancer.
- **Phase 2:**
 - Arms 1, 2, and 3: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with BCG in combination with blinded study product (one of two doses of vesigenurtacel-L or placebo).
 - Arm 4: To evaluate 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with high dose vesigenurtacel-L monotherapy.

Secondary Objectives

Both Phases:

- To evaluate the proportion of patients with recurrence at 3, 6, 12, 18, and 24 months
- To evaluate the proportion of patients with progressive disease at 3, 6, 12, 18, and 24 months
- To evaluate overall disease-free survival
- To evaluate overall survival (OS)
- To evaluate the proportion of patients undergoing post-treatment TURBT or fulguration by 12 and 24 months
- To evaluate the proportion of patients undergoing cystectomy by 12 and 24 months
- To evaluate the proportion of patients with immunologic response of PBMCs via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on CD8+ cells following vesigenurtacel-L vaccination

Phase 2 only:

- To evaluate the safety of the combination of vesigenurtacel-L and BCG
- To evaluate the safety of high dose vesigenurtacel-L monotherapy

Primary Endpoint

- **Phase 1:** Safety and tolerability of monotherapy vaccination with HS-410 in patients with non-muscle invasive bladder cancer.
- **Phase 2:** 1-year disease-free survival in patients with non-muscle invasive bladder cancer treated with BCG in combination with one of two doses of HS-410 or placebo, or with high dose HS-410 without BCG. The 1-year disease-free survival rate is defined as the proportion of patients who are alive and free from recurrence and progression at 12 months following randomization.

Secondary efficacy endpoints:

Both Phases:

- Proportion of patients with recurrence at 3, 6, 12, 18, and 24 months from randomization, estimated based on Kaplan-Meier curves. Recurrence is defined as disease that has recurred to the same extent of disease (ie same stage / severity) or to a lower stage/severity of disease compared to screening.
- Proportion of patients with progressive disease at 3, 6, 12, 18, and 24 months from randomization. Progressive disease is defined as an increase in T stage from TIS or Ta (at screening) to T1 (lamina propria invasion), development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high per the IBCG recommendations.
- Disease-Free survival at 3, 6, 18, and 24 months from randomization. A patient is considered as disease-free at a timepoint if the disease has not recurred nor progressed, and the patient is still alive.
- Overall Disease free survival (DFS): DFS is the time from randomization until the day of disease recurrence or progression
- Overall survival (OS): OS is the time from randomization until the day of death by any cause or censoring
- Proportion of patients undergoing a repeat TURBT by 12 months and by 24 months from randomization
- Proportion of patients undergoing cystectomy by 12 months and by 24 months from randomization
- Immunological response (IR): Peripheral blood immunological response via intracellular cytokine staining (ICS) by ELISPOT of on CD8+ cells following HS-410 vaccination will also be evaluated

Phase 2 only:

- Safety of the combination of vesigenurtacel-L and BCG
- Safety of high dose vesigenurtacel-L monotherapy

Exploratory Endpoints

In patients completing at least 6 weekly doses of study medication, the following exploratory endpoints will be evaluated:

- Immunologic response of PBMCs (analysis of surface markers, CD3, CD4, CD8, degranulation) and stimulation analysis via ICS of IFN- γ , IL-2, TNF α and perforin.
- Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-reg)

- Evaluation of tumour tissue obtained from pre-treatment resection for antigen expression by immunohistochemical analysis
- Evaluation of tumour tissue obtained from repeat biopsy, if clinically indicated, for presence of infiltrating T-lymphocytes
- T cell receptor sequencing of peripheral blood T cells before and during the course of treatment
- Immune cell infiltration and inflammatory cytokine levels in urine (phase 2 only)

Safety Endpoints

In both the phase 1 and 2 components of the study, safety assessments will include medical history, vital signs, physical exam, concomitant therapy and procedures, adverse events (AE) collection, serious adverse event (SAEs), clinical laboratory parameters, urinalysis and electrocardiograms (ECG).

3 Study Methods

3.1 General Study Design and Plan for Phase 1

The phase 1 component of the current protocol will evaluate the safety and tolerability of HS-410, administered at a weekly dose of 1×10^6 cells per 0.5 mL administration. Three patients will initially be enrolled to receive HS-410 weekly for 6 weeks after induction treatment with BCG. After a 1-week vaccine holiday for disease assessment, patients will receive HS-410 for an additional 6 weeks followed by 3 once monthly treatments for a total of 15 vaccinations. Patients will be observed weekly to assess the safety of HS-410. Dosing of the first 3 patients will be staggered by 2-week intervals to allow for safety evaluation before treating additional patients. If the DMC confirms HS-410 appears safe and well-tolerated in the 3 lead-in patients, dosing will be continued to 10 patients. The DMC will reconvene when all 10 patients in Phase 1 have received HS-410 and data is available for the Week 7 safety assessments from at least 6 patients. If this regimen is determined to be safe by the DMC, randomization to Phase 2 will commence.

3.2 General Study Design and Plan for Phase 2

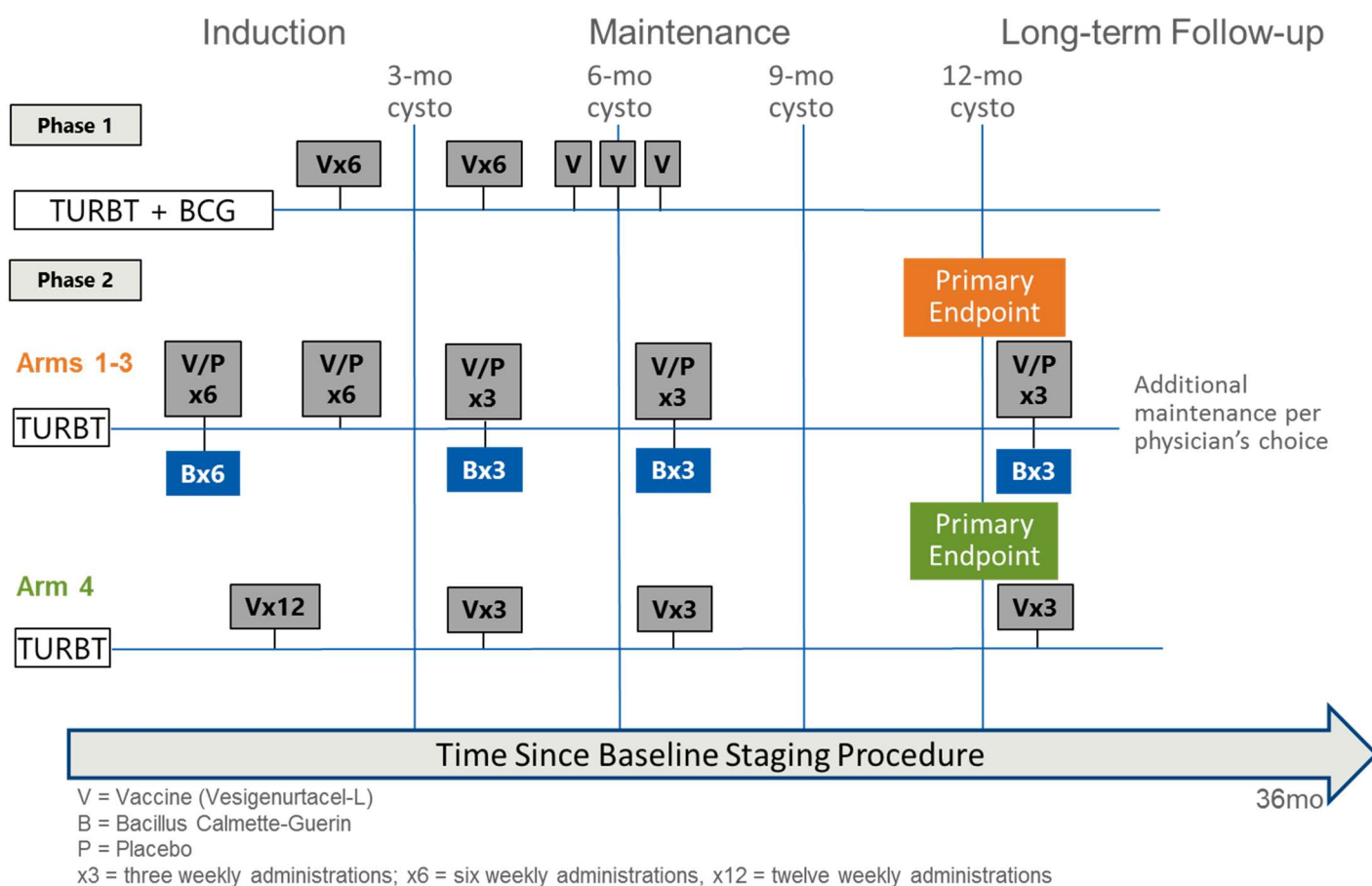
Dosing in Phase 2 will begin when all 10 patients have been dosed in the Phase 1 cohort, at least 6 patients in that cohort have completed the Week 7 safety assessments, and the Data Monitoring Committee (DMC) has met to review this data and agreed it is safe to advance to Phase 2. A total of 100 patients will be assigned to four groups: 75 who will receive BCG will be randomized to arms combining either low dose vesigenurtacel-L (1×10^6 cells), high dose vesigenurtacel-L (1×10^7 cells), or placebo, respectively, with induction and maintenance BCG; 25 who will not receive BCG will be enrolled in the high dose vesigenurtacel-L monotherapy arm.

In the randomized arms, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intravesical BCG and intradermal blinded study product (vesigenurtacel-L or placebo) for 6 weeks followed by 6 weekly injections of blinded study product alone. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly blinded study product injections in combination with intravesical BCG

approximately 3, 6, and 12 months after initiating induction BCG. Patients may receive additional courses of maintenance BCG in long-term follow-up at the investigator's discretion but should not receive any other cancer therapy prior to disease recurrence/progression (Figure 1).

In the monotherapy arm, treatment will commence within 6 weeks of the most-recent TURBT or fulguration for patients with papillary disease and staging procedure for patients with CIS only. Patients will be treated during an induction phase with weekly intradermal vesigenurtacel-L for 12 weeks. During a subsequent maintenance phase, patients will receive an additional three courses of three once-weekly vesigenurtacel-L injections approximately 3, 6, and 12 months after initiating induction vesigenurtacel-L.

Figure 1. Phase 1 and Phase 2 Study Design



3.3 Inclusion-Exclusion Criteria and General Study Population

Patients with non-muscle invasive bladder cancer who have undergone TURBT and are judged to be at an increased risk for recurrence are eligible if they are BCG naive or have completed previous BCG treatment >12 months prior to the most recent TURBT are eligible for both the phase 1 or 2 parts of the study. Patients must meet all of the following inclusion criteria to be enrolled into the study:

Inclusion Criteria

1. Willing and able to sign informed consent and comply with the protocol, including clinic visits to receive weekly vesigenurtacel-L injections for 12 doses followed by either monthly vesigenurtacel-L injections for three months in Phase 1 or three courses of three once-weekly injections in Phase 2.
2. Histologically or cytologically confirmed non-muscle invasive bladder cancer [Ta, T1 or Tis (CIS)]. Papillary disease must have been removed by transurethral resection or fulguration.
3. Either
 - i. High-risk disease, defined as T1 and/or high-grade and/or CIS, *or*
 - ii. Intermediate-risk disease defined as Ta low-grade with at least three of the following four risk factors: multiple tumors, tumor size > 3cm, early recurrence (<1 year from previous staging procedure), or recurrence with a frequency of more than once in any 12 month period.
4. Patients must be BCG naive or have completed previous BCG treatment >12 months prior to the baseline staging procedure.
5. For Phase 2 only: Arms 1, 2, and 3: Suitable, in the opinion of the investigator, to receive a 6-week course of induction intravesical BCG in the adjuvant setting within 6 weeks following the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer. Arm 4: Suitable for monotherapy vaccine administration post-TURBT. For Phase 1 only: Has previously received 3-6 weekly doses of BCG.
6. Age ≥18 years
7. Lab parameters:
 - Albumin ≥2.5 mg/dL
 - Total bilirubin <1.5 mg/dL
 - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 × upper limit of normal (ULN)
 - Serum creatinine ≤2.2 mg/dL or calculated creatinine clearance >35 mL/minute per the Cockcroft-Gault formula
 - White blood cell (WBC) count ≥4,000/mm³ with an absolute neutrophil count ≥1,500/mm³
 - Hemoglobin ≥9 g/dL
 - Platelet count ≥75,000/mm³
8. Women of childbearing potential or men of fathering potential must use adequate birth control measures (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) during the study and for 6 months after receiving the last administration of study medication. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.

Exclusion Criteria

Patients that meet any of the following exclusion criteria are not eligible to be enrolled into the study:

1. Known human immunodeficiency virus (HIV) infection or other immunodeficiency disorders, either primary or acquired
2. Infections or concurrent illness, requiring active therapy
3. Any condition requiring active steroid or other immunosuppressive therapy
4. Active malignancies within 12 months with the exception of those with a negligible risk of metastasis or death treated with expected curative outcome
5. Prior prostatic pelvic radiation within the past 12 months
6. Known history of clinically significant cardiac impairment, congestive heart failure > New York Heart Association (NYHA) cardiac disease classification Class II, unstable angina, or myocardial infarction during the previous three months
7. Known current alcohol or chemical abuse, or mental or psychiatric condition precluding compliance with the protocol
8. Pregnant or nursing
9. Known allergy to soy, egg, or peanut products
10. Receiving another investigational agent (30 day wash-out required prior to first dose)
11. Neo-adjuvant therapy prior to the baseline staging procedure for the current occurrence of non-muscle invasive bladder cancer
12. Prior treatment with a cancer vaccine for this indication
13. Prior vaccination with BCG for tuberculosis disease
14. Prior splenectomy

3.4 Randomisation and Blinding

Patients will be randomized to Arms 1-3 centrally using a randomized block design, stratified for risk of recurrence (strata: high vs. intermediate risk) and CIS (strata: yes vs. no). The intent for stratification is to ensure balance between treatment groups with respect to these important prognostic factors. A block size of 3 was chosen to control for potential imbalance between the three treatment groups. Given the limited sample size, a formal subgroup analysis based on the stratification variables will not be undertaken. Patients who will not receive BCG will be consecutively allocated (non-randomized) into Arm 4 consisting of vaccine monotherapy.

Protocol Version 7.0 was updated to allow a temporary revision to the randomization algorithm due to delays in the batch release of certain doses of vaccine. This allowed the randomization schedule to be temporarily revised from a 1:1:1 randomization to a 1:1 randomization, with one arm being briefly

suspended. The batch was released in time such that this change was never implemented; the randomization algorithm was never changed during the study.

The randomization schedule will be prepared by an independent statistician not otherwise involved with this study, and will be implemented through an interactive web based system. The study will be single-blinded (physician-patient).

3.5 Study Variables

In general, the schedules of assessments (SOA) are divided into an induction and maintenance phase.

In the phase 1 component of the study, the induction phase will consist of 6 weekly vaccine doses, a one week drug free period and then followed by 6 more weekly doses. The maintenance phase will then consist of monthly treatments for 3 doses for up to a total of 15 doses, unless the criteria for treatment discontinuation are met.

In the phase 2 component of the study, the induction phase will consist of 6 weekly HS-410 (or placebo) doses in combination with 6 doses of BCG, followed by 6 weeks of HS-410 or placebo monotherapy with a vaccine holiday on Week 13 to allow for disease assessment. This will be followed by a maintenance phase consisting of 3 courses of three once-weekly injections in combination with intravesical maintenance BCG for a total of 21 doses, unless the criteria for treatment discontinuation are met. Additional maintenance therapy will be at the discretion of the treating physician.

Current Schedule of Assessments for each study are contained in the study protocol.

Study Day and Visit Windows

Patients' time on study will be determined in Study Days. Study Day 1 will be defined as the first day of dosing. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0.

A value obtained on Study Day 1 before administration of study treatment will be considered the baseline value. If a value is not available on Study Day 1, the last available value collected prior to the first dose of study drug will be used as the baseline value. The study date and corresponding study visit will be captured on each case report form (CRF) from which study day will be calculated.

Study Day will be used in the analysis of safety data and efficacy analysis. The protocol allows a 3-day window between randomization and first dose. All efficacy analyses on time-to-event endpoints will consider the date of randomization as Day 1.

4 Sample Size

Phase 1

Phase 1 is designed to provide some indication of safety and tolerability of the low dose of HS-410 as a monotherapy. A sample size of 10 patients in the monotherapy setting is deemed suitable for an assessment of safety.

Phase 2

The objective of the phase 2 study is to compare 1-year disease free survival of two doses of HS-410 + BCG versus BCG + placebo in patients with non-muscle invasive bladder cancer who have undergone TURBT. Given the phase 2 exploratory nature of the study, the overall level of significance will be 0.10, using a one sided test with no adjustment for multiplicity, 75 patients will be randomized in a 1:1:1 (low dose HS-410 plus BCG and high dose HS-410 plus BCG vs. plus BCG + placebo) ratio to yield 69 evaluable (23 patients per arm). 25 patients will be enrolled into the monotherapy arm. Under the assumption that the one-year disease-free survival rate in the control is 60%, the study will have an 80% power to detect a 30% absolute difference between the two experimental groups and the control. Patients will be followed for three years after the last patient has been enrolled and patients will be obtained from approximately 20 participating centers.

5 Statistical Considerations

5.1 General Principles

All statistical analyses will be performed using SAS® Version 9.4 (or later). At the end of the study for both phase 1 and 2, individual data listings and descriptive statistics will be provided by treatment group.

Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), minimum, median, and maximum, unless specified otherwise.

Descriptive statistics for categorical variables will include frequency counts and percentages [N (%)]. Unless stated otherwise, the denominator for percentage calculations will be the number of subjects in the analysis set.

The mean, median (if needed), standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data.

P-values ≥ 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as " <0.001 ". Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

There will be no imputation of missing data.

All data will be listed, sorted by site, treatment and subject, and when appropriate by visit number and/or visit date within subject. All summary tables will include a column for each treatment group in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

5.2 Analysis Populations

5.2.1 Phase 1

Safety Population

- Safety Population is defined as all patients receiving at least one dose of HS-410

5.2.2 Phase 2

Intent-to-Treat (ITT) Population

- The intent-to-Treat (ITT) population is defined as all patients randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received. This population will be used for the primary efficacy analyses, and all analyses of patient disposition, demographics and baseline disease characteristics.

Safety Population

- The safety population will be defined as all randomized patients who receive at least one dose of treatment (BCG, HS-410, or any combination thereof), and be referred to as the “Safety Population”

Per Protocol Population

- The Per Protocol (PP) population is defined as all randomized/enrolled patients in the ITT population who do not have any major protocol deviations. All major protocol deviations will be reviewed by Data Monitoring Committee (DMC) prior to database lock and unblinding. Patients will be excluded from this population if the DMC determines the major protocol deviation may impact on the efficacy outcomes of the patient.

Analysis Population for Exploratory Endpoints

Patients completing at least 6 weekly doses of study medication

5.3 Covariates and Subgroups

There will be no covariate or subgroup analysis in the phase 1 component of this protocol.

For the phase 2 component of the study, the following subgroups may be used to further summarize and evaluate the efficacy endpoints, if sufficient data are available:

- Risk of recurrence (High risk vs intermediate risk)
- Carcinoma in situ (yes vs no)
- Patient immune response
- TNM stage, grade, and severity
- BCG naïve or BCG recurrent; number of prior BCG treatments
- Screening TURBT characteristics (Re-resection TURBT at screening, muscle in specimen)
- Number of prior TURBTs
- Number and size of tumors
- TIL status
- Demographics
- Academic vs. Community practices
- Use of Blue Light cystoscopy
- Use of peri-operative chemotherapy

5.4 Interim Analyses and Data Monitoring

This is a phase 1/2 exploratory trial. Therefore, a formal interim analysis will not be conducted. A Data Monitoring Committee (DMC) will convene after all 10 patients are enrolled in Phase 1 to confirm the study will proceed to Phase 2.

The data collection instrument for this study is a Heat Biologics-defined CRF. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Sponsor's clinical data associates (or designees) will review all source-verified CRFs for logical consistency and will use automated programs to help identify missing data, selected protocol violations, out-of-range data, and other inconsistencies. Data clarification or correction will continue until appropriate resolution. Listings of patient data by dataset and/or by patient will be monitored by the DMC as per the DMC charter.

5.5 Multiple Testing

The proposed phase 1/2 trial is exploratory, focused on learning and hypothesis generation. Therefore, the preservation of the overall significance level is of lesser importance. However, to address the hazards associated with multiple statistical testing, p-values will only be generated for the primary analysis comparing the two doses of the experimental vaccine to the placebo control. The secondary and exploratory endpoints will be presented as point estimates with associated 95%CI.

6 Summary of Study Data

6.1 Subject Disposition

For each of the analysis populations, the number and percentage of patients by treatment group will be provided. In addition, the number of patients in the ITT Population will be summarized by study site and treatment group. The number and percentage of patients discontinuing treatment will be summarized according to reasons of discontinuation as documented in the CRF (e.g. dosing noncompliance, AE, prohibited medications, consent withdrawal). In addition, the number and percentage of patients entering long-term follow-up and completing/discontinuing the follow-up will be presented.

6.2 Protocol Deviations

Major protocol deviations could impact the analysis. Protocol deviations specified in Protocol Section 13.3 will be captured in the CRF and reviewed by a medical monitor for determination of impact on patient inclusion in the Per Protocol population:

- Entered into the study without meeting eligibility criteria
- Developed withdrawal criteria during the study and was not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment
- Failed to collect data necessary to interpret primary endpoints

Protocol deviations will be listed by treatment group, patient number, and categorized according to the deviation reasons. If a significant number of deviations occur, a summary table will be produced showing the number of patients for each deviation reason. Study withdrawal by reasons collected in

the CRF (e.g., eligibility criteria violation, prohibited concomitant treatment, etc.) will also be summarized.

6.3 Demographic and Baseline Variables

For both the phase 1 and 2 parts of the study, the following patient baseline demographics and disease status variables will be summarized by treatment group for the ITT Population:

Demography: Age, sex, race and ethnicity

Stratification factors: Risk of recurrence (High risk vs intermediate risk), carcinoma in situ (yes vs no)

Bladder cancer history: histopathologic type, TNM stage, carcinoma in situ, severity, newly diagnosed disease vs recurrent disease, time from last BCG treatment to screening (for patients with recurrent disease)

Phase 1 Risk assessment: Number of tumors, tumor diameter, prior recurrence rate, category (Ta / T1), concurrent CIS, Grade (WHO 1973), total recurrence score, total progression score

Baseline vital signs: Weight, height, systolic blood pressure, diastolic blood pressure, heart rate, body temperature and respiratory rate

Selected baseline laboratory, including lab values dictating inclusion/exclusion:

- Hematology: White blood cell (WBC) count, neutrophils, platelets, hemoglobin, lymphocytes, red blood cell (RBC) count
- Chemistry: ALT, AST, Alkaline phosphatase, Albumin, total bilirubin, serum creatinine, creatinine clearance

No statistical tests to check homogeneity between treatment groups at baseline will be performed.

6.4 Medical History

Medical history will be coded using MedDRA dictionary version 18 or higher, and will be summarised by MedDRA preferred term and system organ class.

6.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) drug dictionary version March 2013 (or higher), and will be summarised by preferred term and/or ATC class. Medications administered prior to the expected first dose of study will be considered prior medications. Concomitant therapies will be those that are taken on or after Study Day 1 through 30 days after the last dose of study drug. Medications started prior to Study Day 1 and continued into the treatment period will be included in the summary of concomitant therapies. Incidence of prior medication and concomitant therapies will be summarized by preferred term.

7 Efficacy Analyses

All efficacy analyses for recurrence or progression will use standard TNM disease staging, specifically with the following T stage hierarchy: Ta<TIS<T1<T2<T3<T4, and Low Grade<High Grade.

7.1 Primary Efficacy Analysis

The primary efficacy parameter is 1 year DFS and will be conducted on the ITT population. It will be calculated as the proportion of patients in the experimental groups and the control who remain disease free at 1 year. Hypothesis testing on the primary endpoint will be done one-sided at a level of significance of $\alpha = 0.10$ using Fisher's exact test. The absolute difference in proportions, as well as the odds ratio, with the associated 95% confidence intervals will also be presented.

The following rules will be used to determine whether a patient is disease free at 1 year or not

- If a patient has a recurrence before day 394 (ie day 366+28 days) or has dropped out of the study before day 394, then the patient is considered to be not disease free at 1 year.
- If a patient is shown to be free from disease on day 366 +/- 28 days, then the patient is considered to be disease free at 1 year.
- If a patient has no recurrence before day 338 (ie day 366-28 days) and after day 394 (day 366+28 days), then the patient is considered to be disease free at 1 year.

If the analysis of the primary endpoint does not suggest any dose response effect between the two vaccine arms, an exploratory analysis will be conducted where the two vaccine arms will be pooled and compared to the control arm for the primary endpoint (proportion of patients alive and disease-free at one year). The outcome will be presented as OR with 95% CI relative to the control group.

In an additional exploratory analysis, the proportion of patients whose disease has recurred to a lower stage than at screening and the proportion of patients whose disease has recurred to the same extent (or greater) as at screening will be compared between the experimental and control groups and presented as an OR with 95% CI.

7.2 Secondary Efficacy Analyses

For time-to-event endpoints (e.g. DFS, OS), Kaplan-Meier / product limit method will be used to estimate the survival distributions over time, and to estimate median time to event. Where appropriate, inference for time-to-event endpoints will be assessed using the Log-rank test statistic, and the treatment effect will be estimated using Cox proportional hazards model. The assumption of proportional hazards will be assessed graphically.

The following will be analysed using Kaplan-Meier time-to-event methodology:

- Time To Recurrence, defined as the time from randomization to recurrence.
 - Recurrence is defined as disease that has recurred to the same extent of disease (ie same stage / severity) or to a lower stage/severity of disease compared to screening.
 - If recurrence has not occurred in a patient, the date of last disease assessment will be used as the timepoint for censoring.
 - The analysis will be repeated in an exploratory manner where recurrence is defined as only those recurrences to the same extent of disease (or greater) as screening.

- Time To Progression, defined as the time from randomization to progression.
 - Progression is defined as an increase in T stage from CIS or Ta (at screening) to T1 (lamina propria invasion), development of T2 or greater or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high per the IBCG recommendations..
 - If progression has not occurred in a patient, the date of last disease assessment will be used as the timepoint for censoring.

- Disease-Free Survival, defined as the time from randomization to recurrence or progression.
 - If a patient has recurred or progressed, then the first date the recurrence or progression has occurred will be used as the timepoint for the event.
 - If a patient has neither recurred nor progressed, then the date of last disease assessment will be used as the timepoint for censoring.

- Overall Survival, defined as the the time from randomization to death.
 - If a patient is still alive, then the patient will be censored on the date of most recent date known alive.
 - If a patient is lost to follow up, then the patient will be censored on the date last known alive.

- Time to cystectomy, defined as the time from randomization to cystectomy.
 - If a patient has not undergone cystectomy, the patient will be censored on the date of last disease assessment.

- Burden of repeat TURBT, defined as the proportion of patients with no repeat TURBT vs 1 TURBT vs 2 TURBT vs 3 TURBT etc within 12 months since randomization (ie day 366 or earlier), within 18 months since randomization (ie day 548 or earlier) and within 24 months since randomization (ie day 731 or earlier).

For time to recurrence, time to progression, disease-free survival and overall survival, the Kaplan-Meier estimates on the proportion of patients free from the event of interest at 3, 6, 9, 12, 18 and 24 months from randomization will be presented.

For time to cystectomy, the Kaplan-Meier estimates on the proportion of patients with cystectomy at 12, 18 and 24 months from randomization will be presented. In addition, the time to cystectomy from original TURBT will be analysed in a similar way, and the data will be presented as sensitivity analysis.

For intensity of repeat TURBT, the same analysis will be repeated using the 12, 18 and 24 months since original TURBT, as sensitivity analysis.

7.3 Exploratory Analyses

All primary and secondary efficacy endpoints will be reanalysed in the Per-protocol population.

If available in a suitable timeframe before reporting, immunologic response data will be listed in the CSR. If applicable, summaries and exploratory analyses will be specified in a separate analysis plan and presented in a separate report.

The following endpoints will be analysed:

- immunologic response of PBMCs,
- total PBMC counts by flow cytometry,
- evaluation of tumour tissue obtained from pre-treatment resection for antigen expression by immunohistochemical analysis,
- evaluation of tumour tissue obtained from repeat biopsy, if clinically indicated, for presence of infiltrating T-lymphocytes,
- T cell receptor sequencing of peripheral blood T cells before and during the course of treatment
- Tissue immune cell infiltration, and inflammatory cytokine levels in urine

8 Safety Analyses

Safety comparisons will be performed on all patients who received at least one dose of experimental treatment in both phases of the study. The safety variables to be analyzed include vital sign measurements, AEs, ECGs, routine hematology, coagulation factors, serum chemistry, urinalysis, and deaths. Unless otherwise noted, safety variables will be tabulated by descriptive statistics (n, mean, median, SD, minimum, and maximum; or n and percent) using the Safety Population. When calculating the incidence of adverse events, or any sub-classification thereof by treatment, time period, severity, etc., each subject will only be counted once and any repetitions will be ignored; the denominator will be the total population (or treatment group, as applicable) size. A descriptive summary of all Treatment emergent adverse events (TEAEs) by system organ class and preferred term will be provided.

8.1 Extent of Exposure

Treatment exposure will be summarized by treatment group, in the following ways:

- (1) Number of doses of vesigenurtacel in phase I and vesigenurtacel/placebo in each arm in phase II, overall and also separately for induction phase and for maintenance phase.
- (2) Cumulative doses of vesigenurtacel in phase I and vesigenurtacel/placebo in each arm in phase II, overall and also separately for induction phase and for maintenance phase.
- (3) Cumulative BCG dose in arms 1,2,3 in phase II, overall and also separately for induction phase and for maintenance phase.
- (4) Number of patients receiving the full dose vs partial dose of vesigenurtacel and BCG in induction and maintenance up to 12 months since the start of induction of BCG. The number of patients receiving additional maintenance (as per physician's choice) beyond 12 months from the start of induction of BCG will also be summarised.
- (5) Number of dose reductions / dose delays in vesigenurtacel and BCG

8.2 Adverse Events

TEAEs will be defined as events that occur on or after the first dose of study medication. The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary will be used for the coding of AEs (version 18.0 or higher). The severity of TEAEs will be graded on a scale of 1 to 5 according to the adult NCI Common Terminology Criteria for Adverse Events (CTCAE version 4.0) where higher grades indicate events of higher severity. Adverse events will be summarized by grade according to the worst grade experienced. TEAEs, serious or CTCAE grades -5 TEAEs, and TEAEs related to therapy will be summarized overall and by system organ class and preferred term by treatment group. A listing of AEs leading to treatment discontinuation including the patient number, site, treatment group, start date and study day of AE, severity, relationship to study regimen, action taken, and outcome of AE will be provided. Additional summary table summarizing preferred term may be provided if warranted.

For summary purposes, AEs will be defined as all reported events with a start date on or after Study Day 1. All AEs are collected through 30 days post last dose (treatment-emergent AEs). All AEs will have their relationship to study drug (BCG or HS-410) assessed by the investigator as related or not related. Adverse events will be categorized and summarized according to their highest relationship to study drug.

8.3 Serious Adverse Events, Premature Treatment Discontinuation and Deaths

A listing of SAEs including the patient number, site, treatment group, start date and study day of SAE, severity, relationship to study drug, action taken, and outcome of SAE will be provided. Additional summary table by preferred term may be provided if warranted.

A listing of deaths including the patient number, site, treatment group, date and study day of death, and cause of death will be provided.

8.4 Clinical Laboratory Evaluations

Hematology Results

The hematology values to be measured include hemoglobin, hematocrit, platelet counts, red blood cell (RBC) count, lymphocyte count, neutrophil count, and white blood cell (WBC) count. Where applicable, Laboratory results for hemoglobin, platelet count, lymphocyte counts, neutrophil counts, and WBC counts will be classified according to the NCI CTCAE version 4.03, and shift tables of baseline grades vs worst post-baseline grades for these parameters will be presented. For other parameters, shift tables of low/normal/high at baseline vs post-baseline may be presented where appropriate. Laboratory values and change from baseline for selected parameters may also be summarised by visit.

Serum Chemistry Results

The serum chemistry values to be measured include sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, bicarbonate, lactate dehydrogenase, and glucose. Where applicable, laboratory results will be classified according to the NCI CTCAE version 4.03, and shift tables of baseline grades vs worst post-baseline grades for these parameters will be presented. For other parameters, shift tables of low/normal/high at baseline vs post-baseline may be presented where appropriate. Laboratory values and change from baseline for selected parameters may also be summarised by visit.

8.5 Other Safety Measures

Urinalysis

Patients will have urine samples collected for routine urinalysis. The urinalysis will include colour, appearance, and dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, and pH. Shift table of baseline vs post-baseline, or summary statistics of actual values and change from baseline values at each visit, will be presented accordingly.

ECG

The following parameters from 12-lead electrocardiograms will be evaluated: heart rate, PR interval, QRS duration, QT interval, and QTcF interval. Descriptive statistics for these parameters will be summarised at baseline. The values and change from baseline will be summarised at weeks 7, 14 and 29 in phase I, and at week 56 for phase II.

The following changes will be flagged in listings:

- Absolute QTc interval prolongation:
 - QTc interval > 450
 - QTc interval > 480
 - QTc interval > 500
- Change from baseline in QTc interval:
 - QTc interval increases from baseline >30
 - QTc interval increases from baseline >60

Injection Site Reactions

Injection site reactions will be summarized by the type of reaction (Pain, erythema, edema, pruritus, warmth, hematoma, induration, other) and by grade.

Incidence of injection site reactions leading to dose interruption and to drug discontinuation will be summarized, where appropriate.

Time to first onset of injection site reaction (i.e. the number of vesigenurtacel administered by the onset of the first injection site reaction) will be calculated using Kaplan-Meier methodology. Number of patients with more than one injection site reactions will also be presented.

Vital Signs

Vital sign measurements collected include blood pressure, heart rate, respirations, and body temperature. Body temperature will be collected in °F or °C, but reported in °C. Data will be converted to °C for summarization purposes using the following formula: °C = 5/9 (°F-32). Vital signs and change from baseline in vital signs will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) at each scheduled visit.

Appendix 1: List of Planned Figures and Tables

9 References

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