STATISTICAL ANALYSIS PLAN

TITLE PAGE

AN OPEN-LABEL NON-RANDOMIZED, MULTI-CENTER PHASE-2 STUDY OF CONVECTION-ENHANCED DELIVERY (CED) OF MDNA55 IN ADULTS WITH RECURRENT OR PROGRESSIVE GLIOBLASTOMA

Final Version 2.0: OCT 23, 2019

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DECLARATION

I, the undersigned, declare that I have prepared the statistical analysis plan along with TLF mockups and that to the best of my knowledge this document is internally consistent with protocol and scientifically rational.

[redacted]

Oct 23, 2019

[redacted]

LIST OF ABBREVIATION

Abbreviation or special term	Explanation
AE	Adverse Event
CED	Convection-Enhanced Delivery
CI	Confidence Interval
CNS	Central Nervous System
cpIL-4	circularly permuted version of IL-4
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOCB	Duration of Clinical Benefit
DOR	Duration of Response
ECG	Electrocardiogram
FDA	Food and Drug Administration
GB	Glioblastoma
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IL4R	IL-4 receptor
INR	International Normalized Ratio
ITT	Intent to Treat
IV	Intravenous(ly)
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
MDNA55	Study drug; IL-4PE; previously called NBI 3001, PRX321
MGMT	O^6-methylguanine-methyltransferase
mITT	Modified Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mRANO	Modified RANO
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Pseudomonas exotoxin
PFS	Progression Free Survival

Abbreviation or special term	Explanation
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RANO	Response Assessment in Neuro-Oncology (criteria)
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-emergent Adverse Event
TME	Tumor Micro-Environment
TRAM	Tumor Response Assessment Map
US	United States
WBC	White Blood Cell (count)
WHO	World Health Organization

1. INTRODUCTION

The study drug, MDNA55, is a fusion protein consisting of a targeting domain linked to a pro-apoptotic cell-killing payload. It was discovered and developed by Drs. Raj Puri (United States [US] Food and Drug Administration [FDA]) and Ira Pastan (National Cancer Institute "NCI") and has been described by various researchers in over 50 publications. It is a therapeutic agent that selectively targets cancer cells that over-express the interleukin-4 receptor (IL4R). The targeting domain is an engineered circularly permuted version of interleukin-4 (cpIL-4) which is genetically fused to potent payload comprised of a truncated version of the bacterial toxin, Pseudomonas aeruginosa exotoxin (PE) A (Kreitman et al., 1994). It was developed for the treatment of glioblastoma (GB) and other adult and pediatric central nervous system (CNS) cancers including immunosuppressive cells of the glioblastoma tumor microenvironment (TME) that frequently over-express the IL-4 receptor (IL4R; Puri et al., 1994; Kohanbash et al., 2013).

The mechanism of action of MDNA55 is well documented (Kreitman et al., 1994; Rand et al., 2000; Puri et al., 2009) and is depicted in **Figure 1**.

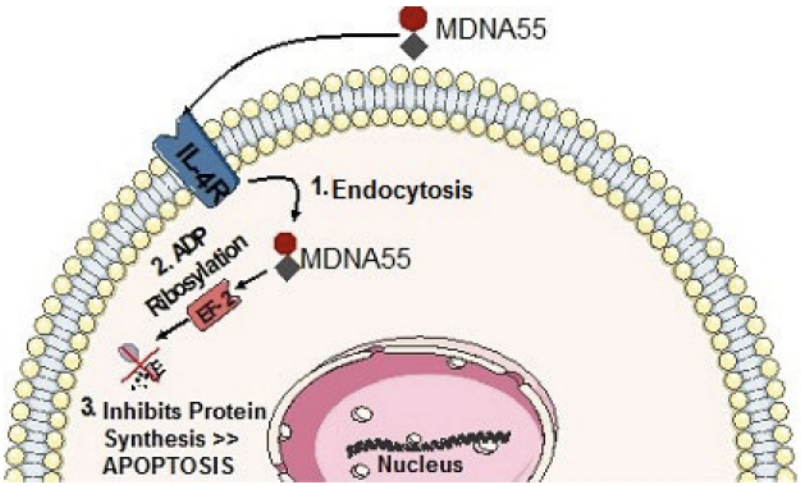

Figure 1: Schematic of MDNA55 Mechanism of Action

MDNA55 binds to IL4R overexpressed on the surface of tumor cells and the entire complex is endocytosed. Following cleavage and activation by furin-like proteases found in high concentrations in the endosome of cancer cells, the catalytic domain of the truncated PE is released into the cytosol where it induces cell death via adenosine diphosphate (ADP)-ribosylation of the Elongation Factor-2 and induction of apoptosis through caspase activation (Shapira and Benhar, 2010).

The purpose of this statistical analysis plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol MDNA55-05, Protocol Version 6.1 "An Open-Label Non-Randomized, Multi-Center Phase-2 Study of Convection-Enhanced Delivery (CED) of MDNA55 in Adults with Recurrent or Progressive Glioblastoma" dated July 19, 2019 for Final analysis. The table of contents and templates for the tables, figures

and listings (TFLs) will be produced in a separate document. Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonization (ICH) E9. Unless otherwise specified, all data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

2. OBJECTIVES

Primary Objective

- To assess overall survival (OS).

Secondary Objectives

The secondary objectives of this study are:

- To assess the effect of IL4-R status on overall survival (OS);
- To assess the safety of MDNA55 following CED;
- To determine the objective response rate (ORR) per Response Assessment in Neuro-Oncology (RANO)-based criteria incorporating advanced imaging modalities (conditional on availability of advanced imaging data);
- To assess progression-free survival (PFS).

Exploratory Objectives

The exploratory objectives of this study are:

- To assess the pharmacokinetics (PK) of MDNA55 in peripheral plasma;
- To assess serum anti-MDNA55 antibody titers and, if elevated, determine neutralizing antibody titers;
- To determine the relationship between clinical outcomes and response assessment status by different sets of imaging-based response criteria;
- To perform additional ad hoc efficacy and safety analyses as needed based on the data acquired in this study;
- To assess the performance of the Brainlab catheter during infusion in terms of distribution and convection of the infusate using real time MRI monitoring.

3. STUDY DESIGN

3.1 General Study Design

This is a single-arm, open-label, multicenter study in approximately 52 adults (at least 46 evaluable) with GB that has recurred or progressed (according to standard RANO criteria). The study will be conducted at up to 12 clinical sites following institutional review board approval and completion of informed consent.

Eligible subjects will undergo surgery associated with catheter placement at which time a tissue biopsy will also be performed. MDNA55 will be infused with the objective of achieving coverage of the tumor and the peritumoral margin to the maximum extent possible as indicated by distribution of a co-infused gadolinium tracer observed by MRI. Pre-treatment catheter trajectory planning will be performed with aim to place up to 4 catheters but a minimum of 2, depending upon the tumor size. Planning for catheter placement will only target the enhancing region of the tumor on MRI.

Study duration is 12 months for each subject with the day of catheter placement/ start of infusion being designated as Day 0.

Post-treatment follow-up assessment of safety will be performed 14 days after CED infusion. Thereafter, efficacy and safety assessments will be performed at 30, 60, 90 and 120 days after CED infusion and every 8 weeks thereafter until 360 days of active follow up have been completed. Subjects who discontinue before the Day 360 visit will undergo all the procedures scheduled for the Day 360 visit at the time of discontinuation.

Subjects who complete the Day 360 assessment without disease progression or discontinue early without disease progression will continue to be followed for disease status until progression where possible. After progression (on study or during post-study follow-up), subjects will continue to be followed, where possible, for survival, post-study treatment(s) for GB and imaging for GB until death (or termination of data collection by the Sponsor or withdrawal of consent by the subject).

3.2 Randomization and Blinding

This study is a single-arm design. All subjects will receive active treatment. No randomization will be performed. No blinding procedures are employed.

3.3 Study Treatment

The concentrations of MDNA55 evaluated in this study will be 1.5, 3, 6, and 9 µg/mL administered in various volumes that do not exceed 240 µg (the established maximum tolerated dose of MDNA55).

Infusion via each catheter will be initiated at the rate of 3 µL/min/catheter and gradually increased in a stepwise manner. The infusion flow rate can be adjusted at the discretion of the Investigator during real time MRI (with subject maintained under anesthesia) provided that the flow rate per catheter does not exceed 10 µL/min. All functioning catheters should be convicting

at similar flow rates. The flow rate should be established such that the duration of infusion is at least 24 hours to a maximum of approximately 48 hours. In the event that only one catheter is functioning, the flow rate may be increased to complete infusion in 48 hours or less but greater than 24 hours. After the real-time MRI infusion monitoring period is completed, the remainder of the infusion will continue with the subject awake. MRI will be performed upon completion of infusion as a final evaluation of MDNA55 infusate distribution.

At the discretion of the Investigator, a subject may be eligible to receive a second administration of MDNA55.

A detailed description of procedures and assessments to be conducted during this study is summarized in the schedule of study assessments in Table 2, taken from the latest protocol version (Version 6.1).

Table 2: Schedule of Events

Evaluation	Screen	Hospitalization				Day 14	Day 30, 60, 90 120, then q8w	Long Term F/up
		Before Catheter Placement	Catheter Placement	CED Infusion	End of CED Infusion			
Day	-14 to 0	-24 hrs to 0	0	0-2	1-2 a	14 a	a, b, c	p
Informed Consent [d]	X							
Hospital Registration		X						
Medical/Oncological History	X	X			X			
Operative & Pathology Reports for Index Tumor (resection/biopsy) [e]		X						
Confirmation of archived tissue being available for biomarker analysis [f]	X							
MRI	X[g1]	X[g2]	X[g3]		XX[g4]		X[g5]	
CT	X[g6]							
Physical Exam, KPS	X	X			X[q]	X	X	
Vital Signs (pulse, respiratory rate, weight and blood pressure)	X	X	X[r]	X[r]	X[s]	X	X	
Neurological Exam	X	X			X	X	X	
Standard 12-lead Electrocardiogram (triplicate assessment)	X				X[t]			
Serum Pregnancy Test [h1]	X						X	
Hematology / Serum Chemistry [h2]	X				X[u]	X	X	
Coagulation [h3]	X				X[u]	X	X	
Urinalysis [h4]	X							
Pharmacokinetics [i1]	X			X		X		
Immunogenicity [i2]	X					X	X	
Pre-anesthesia blood sample [i3]			X					
Baseline Conditions j	X	X						
Pharmacy Preparation of Infusate [l]			X	X				
Catheter placement with biopsy [k]			X					
CED Infusion: MDNA55/Gadolinium [k]				X				
Catheter(s) Removal [m]					X			

Concomitant Meds/Corticosteroids [n]	X	X	X	X	X	X	X	
Adverse Events [o]			X	X	X	X	X	
Telephone Contact [p]								X

Treatment or visit delays for weekends, public holidays or weather conditions do not constitute a protocol violation

a Safety assessed after initiation of infusion (during and following CED infusion throughout entire hospitalization period) and safety follow-up to be performed on Days 14 and 30 (± 3 days), and 60, 90, 120, 180, 240, 300 and 360 (± 7 days).

b Scheduled follow-up to be performed with MRI up to 12 months after CED infusion on Day 30 (± 3 days) and Days 60, 90 and 120, then q8w until Day360 (± 7 days) NOTE: at the Day 300 visit only MRI, physical exam/neurological exam/KPS need be performed.

c Subjects who discontinue before the Day 360 visit will undergo all the procedures scheduled for the Day 360 visit if early termination is between follow-up visit time points with the specific provision that MRI will not be required if last MRI performed was within 2 weeks prior to the early termination date. When early termination is in line with a study follow up visit time point that visit will be considered the early termination time point and no other assessments apart from the respective visit date assessments will be required.

d ICF can be signed in advanced of the 14 day screening period.

e Operative report to be accessioned.

f Archived tissue from the resection of the initial GB diagnosis required for biomarker analysis including IL4R IHC, MGMT DNA methylation, and other translational biomarkers.

g All MRIs acquired throughout entire study schedule will follow will be performed according to imaging protocols outlined in the study specific Image Acquisition Guide.

g1 Screening MRI to be subject to independent assessment to verify objective radiologic tumor characteristics [e.g. tumor size; subjects must have tumor diameter of ≥ 1 cm x ≥ 1 cm (minimum) to 4 cm in any direction, etc.]; additional image reviews of screening MRI pertaining to evaluation of suitability of subjects for convection may be performed by CED experts; if subject approved for enrollment, screening MRI will also be used for catheter placement planning using iPlan® Flow.

g2 Pre-operative planning MRI can be performed in one or two MRI exams as required, based on local capabilities; Timing of planning images to support catheter trajectory planning is described in Table 6; Planning MRI images will be registered with iPlan® Flow Infusion planning software to support finalization of catheter trajectory plan.

g3 On Day 0 MRI performed following catheter placement prior to the start of CED infusion as well as during infusion for real-time MRI infusion monitoring (for approximately 1 hour while subject is maintained under anesthesia) (see Section 6.3 for CED infusion procedure).

g4 On Day 1 or Day 2 (depending on duration of infusion) MRI performed within 4 hours (ideally within 2 hours) after completion of infusion relative to infusion end date/time; another MRI performed within 18-30 hours after completion of infusion prior to subject being discharged from the hospital.

g5 MRI performed as part of the scheduled follow-up visits on Days 30, 60, 90, 120 and then q8w thereafter until Day 360 / early termination. For subjects who are progression free, MRIs will continue as per the institution's standard of care schedule until confirmed disease progression.

g6 CT scan acquisition only required when no CT scan is available within 3 months of planned infusion.

h1 Females of childbearing potential only at Screening, Days 30 and Day 180

h2 Hematology: hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, and WBC differential; Serum chemistry: AST, ALT, lactate dehydrogenase (LDH), total bilirubin, indirect bilirubin, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, uric acid, and glucose.

h3 Coagulation: prothrombin time (PT)/PTT/INR (PTT, corrected, if necessary).

h4 Urinalysis: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite. Microscopy required only to follow-up clinically significant abnormal findings.

i1 PK assessed at Screening (baseline), as soon as possible but not more than 1 hour following infusion end time, approximately 3 hours following completion of infusion and then (after the ~3 hour sample collection) every 6 hours ± 2 hours until 24 hours or until subject is discharged from the hospital (whichever occurs first) and at Day 14.

i2 Immunogenicity assessed at Screening (baseline) and at Days 14, 30, 120, 240, and 360/early termination.

i3 Pre-anesthesia blood draw (within 1 hour of subject be placed under anesthesia), this blood sample collection and processing will use a study specific sample collection kit and require immediate (same day) shipment to central laboratory.

J Baseline conditions/symptoms will be collected from Screening until Day 0 before subject is anesthetized for catheter placement surgery; any baseline condition or symptom noted prior to catheter placement will be recorded in the Medical History.

k see Section 6.3; prior to catheter insertion, core tumor biopsy samples (at least 3 cores) will be collected, if the neurosurgeon determines it is possible to harvest viable tumor tissue from along the planned trajectory of the CED catheter(s); biopsy sample tissue collection and processing will use a study specific sample collection kit and require immediate shipment to the central laboratory.

l see Study Pharmacy Manual for infusate preparation and dispensing instructions.

m Following completion of infusion (only after the end of infusion MRI and at any time prior to subject's discharge from the hospital), the catheters can be removed, and the incisions closed in accordance with institutional practice. Removal of catheters must be performed by a delegated neurosurgeon.

n All concomitant medications will be collected on the Electronic Data capture (EDC) system from the date of informed consent through 30-day safety period. Thereafter, concomitant medications associated with treatment-related SAEs and detailed anti-tumor therapy will be collected. Corticosteroid use will be collected until Day 60 or early withdrawal.

o All AEs will be collected from catheter placement through the end of study visit and all AEs and SAEs will be followed until resolution, stabilization, data cut-off, or death.

p Subjects who complete the Day 360 assessment without disease progression or discontinue early without disease progression will continue to be followed for disease status until progression. After progression (documented on study or during post-study follow-up), subjects will continue to be followed for survival, post-study treatment(s) for GB and imaging for GB, where possible, until death (or termination of data collection by the Sponsor or withdrawal of consent by the subject).

q Physical exam and KPS assessments will be performed after completion of infusion when the subject is ambulatory prior to hospital discharge.

r Vital signs monitoring (without weight parameter) will be performed according to institutional best practice throughout entire surgical workflow for catheter placement and CED infusion; study specific vital signs check points during the surgical workflow are prior to initiation of anesthesia, following placement of all catheters but prior to patient being loaded into MRI machine for the real-time infusion monitoring segment and approximately 1 hour post initiation of infusion; NOTE: Site will record any abnormal vitals observed at any time during surgical vital signs monitoring as unscheduled findings.

s Vital signs taken after completion of infusion when the subject is ambulatory prior to hospital discharge.

t ECG (triplicate assessment) will be performed at Screening and immediately following completion of infusion (within 2 hours of infusion end time); triplicate assessment in 3 immediate traces.

u Blood samples for hematology, serum chemistry, and coagulation (Section 7.2.1) shall be taken in parallel with either the PK blood collection that is performed within 1 hour following completion of infusion or the PK blood collection that is performed ~3 hours following completion of infusion.

4. STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

- Overall survival, defined as the time from treatment until death.

4.2 Secondary Efficacy Endpoints

- Overall survival by tumor IL4-R status;
    - IL4-R status of tumor will be determined based on archived biopsy from the time of initial diagnosis;
- ORR as determined by an independent central review according to RANO- based criteria which may incorporate advanced imaging modalities (e.g. diffusion, perfusion and/or TRAMs, conditional upon advanced imaging data being available);
    - ORR is defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR) out of all treated subjects;
- PFS, defined as the time from treatment until disease progression or death.

4.3 Other Efficacy Endpoints

- Duration of response (DOR). Defined as the time from first response until disease progression (per RANO-based criteria and as determined by an independent central review) or death among those subjects achieving a complete response (CR) or partial response (PR) to treatment;
- Duration of clinical benefit (DOCB). Defined as the time from first response or disease stabilization until disease progression (per RANO-based criteria and as determined by an independent central review) or death among those subjects achieving tumor control: complete response (CR), partial response (PR), or stable disease (SD);
- To determine the Tumor Control Rate (TCR) defined as the proportion of subjects in whom the best overall response is determined as complete response (CR), partial response (PR) or stable disease (SD) based on different sets of imaging-based response criteria. Use of sub-therapeutic doses of Avastin will also be considered in determination of TCR (and will result in a variant of the TCR being calculated);
- Time to Tumor Progression (TTP). Defined as the time from treatment until tumor progression; does not include death.

4.4 Exploratory Endpoints:

- To determine the relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and tumor response category using different sets of imaging-based response criteria;

- To determine the relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP, TCR) and IL4R expression status;
- To determine the relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and various prognostic factors (i.e., age, sex, KPS, MGMT status, etc);
- To determine the relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and use of concomitant medication (i.e., Avastin, steroids);
- To determine the relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and various treatment and drug distribution parameters (i.e., MDNA55 concentration, total dose, volume of infusion, percent tumor coverage, etc.);
- To assess the performance of Brainlab catheter during infusion through real time MRI monitoring;

Note: All exploratory analyses will be conditional upon data being available.

4.5 Safety Endpoints

The safety assessments to evaluate the overall safety of MDNA55-05 will include:

- Serious adverse events (SAEs) and treatment emergent adverse events (TEAEs);
- Vital signs;
- Physical examinations;
- Neurological examinations;
- Electrocardiogram (ECG);
- Clinical laboratory results (haematology, serum chemistry, coagulation, urinalysis);
- Karnofsky Performance Status (KPS).

4.6 Other Endpoints

- MDNA55 PK parameters in peripheral plasma;
- Anti-MDNA55 antibody (ADA) titer in serum;
- Neutralizing antibody (NAb) titer (if anti-MDNA55 titer is observed).

5. STUDY POPULATIONS

5.1 Intent to Treat Population (ITT)/Safety

An ITT population will comprise all subjects who sign the ICF and who receive any amount of study drug.

5.2 Modified Intent to Treat Population (mITT)

A modified ITT population for secondary response analyses (mITT) will comprise all subjects who receive any amount of study drug and have adequate imaging (at least 1 post-treatment scan) and clinical data for the ORR analysis.

5.3 Per Protocol Population (PP)

The PP population will comprise all subjects in the mITT population who also have no major protocol violations during the study. Efficacy analyses will be conducted on this population in support of the primary efficacy results.

5.4 IL4R Population

The IL4R analysis population will be those in the ITT population who have archived tissue or adequate tissue available for analysis and will be used for efficacy analyses in subgroups according to IL4R expression status.

5.5 PK Population

The PK Population may include all subjects who received any dose of MDNA55 and who had at least one post-treatment PK sample available. Subjects who received the highest dose concentrations (6 and 9 ug/mL) will be analysed first. If all results from this cohort are Below Level of Quantitation (BLQ), consistent with historical data showing no evidence of systemic exposure with MDNA55, no further subjects will be analysed unless requested by a regulatory authority.

5.6 Anti-Drug-Antibody Population

The ADA Population will include all subjects who received any dose of MDNA55 and who had a baseline (pre-treatment) and at least one post-treatment ADA sample available.

Neutralizing antibody titers will be assessed in the ADA population as appropriate and applicable.

6. STATISTICAL ANALYSIS CONSIDERATIONS

6.1 Handling of Missing Data and Dropout

All available data will be used, and no efficacy data will be imputed. For the analyses of response, subjects with baseline assessments but no post-treatment assessments will be non-evaluable. For time to event variables, subjects not known to have experienced an event at the time of analysis will be censored.

6.2 Handling of Missing or Incomplete Date

To handle missing or partial AE and concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the month is unknown, then:
   a) If the year matches the year of the dose date, then impute the month and day of the dose date.
   b) Otherwise, assign "January."
2. If the day is unknown, then:
   a) If the month and year match the month and year of the first dose date, then impute the day of the dose date.
   b) Otherwise, assign "01."

For partial end dates:

1. If the month is unknown, then assign "December."
2. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the AE (or medication) is treatment emergent (or concomitant medication).
2. If the start date is missing but the stop date is not missing and is on or after the day of catheter placement, then the most conservative approach is taken and the AE (or medication) is treatment emergent (or concomitant medication).
3. If the start date is missing but the stop date is not missing and is before catheter placement and after the date of signed informed consent, then the medication is before treatment (or prior medication). Note: this is not applicable to AEs as all AE collection start from date/time of catheter placement.
4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken, and medication concomitant while the AE is defined by start date.

6.3 Visit Windowing

Not applicable for this study.

6.4 Baseline Definition

The baseline value is defined as the last non missing assessment prior to catheter placement.

6.5 Derived Variables

Change from Baseline is defined as Post baseline value – Baseline value.

Percent Change from Baseline is defined as the (Post baseline value – Baseline value/ Baseline value) *100.

Study day is defined as the number of days from the date of catheter placement:

Study Day = (Target Date - Date of catheter placement) + 1 if target date is greater than or equal to the date of catheter placement.

or

Study Day = (Target Date – Date of catheter placement) if target date is less than date of catheter placement.

7. STATISTICAL METHODOLOGIES AND ANALYSES

7.1 General Statistical Conventions

All statistical analysis will be performed using SAS® version 9.3 or above. Summary tables (descriptive statistics and/or frequency tables) will be provided for baseline variables, efficacy variables and safety variables. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, minimum, maximum, median. Frequency counts and percentage of subjects within each category will be provided for categorical data. Summaries will be provided for overall treatment.

Decimal Precision Convention: Means and medians will be reported to one decimal place more than the raw data. Standard deviation will be reported to two more decimal places than the raw value. The minimum and maximum will be reported to the same decimal as the raw data. In case of n<2, where n indicates the number of evaluable subjects at the particular time point, only n, mean, minimum and maximum will be displayed. The statistic "Missing" will also be evaluated by enumerating the number of missing entries/subjects, if any at that visit, and presented as a summary statistic only for the resulting time points.

Categorical variables will be summarized using the frequency count and the percentage of subjects in each category. All percentages will be rounded to one decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X). To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects are in that category. Counts of zero in any category will be presented as "0". Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group will be the denominator.

[redacted]

7.2 Subject Disposition

Subject disposition information will be summarized according to the following:

- number of subjects who are enrolled:
    - overall
    - according to MDNA55 concentration (1.5, 3, 6, and 9 μg/mL)
    - according to protocol version
- number and percent of subjects who completed the 360 day study visit
- number of screen failure subjects
- number of subjects who are treated

In addition, the number of treated subjects who discontinued from the study, and the reasons for discontinuing from the study will also be summarized. In the summary table, percentages will be calculated using the number of enrolled subjects as the denominator. All the population counts and percentages will be displayed in the summary.

Subject disposition data will be listed including dose (concentration, volume and total dose), enrollment date (consent date), protocol version consented under, infusion start date/time, infusion end/date and time, the withdrawal/completion date, and reason for withdrawal.

7.3 Protocol Deviations

Major protocol deviations will be summarized by deviation category. This analysis will be performed for all subjects. All protocol deviations will be listed by subject.

7.4 Demographics and Baseline Characteristics

Demographic and baseline Subject characteristics will be summarized based on the ITT population and according to the following categories:

- Overall;
- By concentration of MDNA55 administered (1.5, 3, 6, 9 μg/mL);
- By low and high total dose of MDNA55 administered (based on median);
- By IL4R status ($IL4R^{High}$, $IL4R^{Low}$).

All demographic and other baseline characteristics will be provided in a listing for ITT Population. Categorical variables will be summarized using frequencies while continuous variables will be summarized using mean, SD, median, minimum, and maximum.

7.4.1 Demographics

The following demographic characteristics will be summarized

- Age (years)
- Sex
- Ethnicity
- Race

Age will be calculated as: age = Integer ≤ [(ICF date – Date of Birth + 1) / 365.25]

7.4.2 Baseline and Disease Characteristics

The following baseline characteristics of the underlying disease will be summarized:

- Karnofsky Performance Score.
- MGMT Status (positive/methylated or negative/unmethylated)
- Steroid use (Yes, No).
- GBM grade
- Diagnostic method of Glioblastoma (CT, MRI, Biopsy).
- Prior Glioblastoma treatment (Surgery, Radiotherapy, Temozolomide, Other Chemotherapy, Investigational, Other).
- Initial diagnosis to 1st relapse (months)
- Initial diagnosis to current relapse (months)
- Initial diagnosis to start of MDNA55 treatment (months)
- Number of prior relapses (1 or 2)
- Max tumor diameter at baseline (cm)
- Tumor volume at baseline (cm3)

- Lymphocyte count
- Height (cm)
- Weight (kg)
- Body mass index (BMI)

7.5 Medical History

Medical history will be summarized by the number and percentage of subjects in each system organ class (SOC), preferred term (PT), and overall using the safety population. Subjects will be counted only once at the preferred term (PT), only once at the system organ class (SOC), and only once at subject level for the counting of total number of subjects with a medical history term. Counts will be presented in descending frequency of SOC term for the treatment column unless otherwise specified. Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) latest version.

Listings of Medical History will be provided for using the Safety Population.

7.6 Prior and Concomitant Medications/ Corticosteroids

Prior and concomitant medications will be coded using World Health Organization-Drug Dictionary and will be categorized by preferred name and ATC level 4 class per WHO, which will be summarized using the Safety Population for each of the 3 periods: prior to catheter placement, during infusion and post end of infusion. Listings of all prior and concomitant medications will be provided for using the Safety Population.

Prior Medications/Corticosteroid: Prior medications will include any medication having a stop date/time prior to catheter placement.

Concomitant Medications/Corticosteroid: Concomitant medications, are any medications having a stop date/time after catheter placement or ongoing.

All concomitant medications/corticosteroids will be reconciled accordingly at point of subject early withdrawal /or study completion as either having a stop date or ongoing.

7.7 Efficacy Analyses

7.7.1 Primary Efficacy Analyses

The primary efficacy assessment will be overall survival defined as the date of catheter placement until death from any cause. Subjects who are not known to have died at the time of the analysis will be censored at the date of last contact.

OS= Date of death/Censored – Date of catheter placement +1.

Survival rates at 6, 9, and 12 months and their exact 95% CI for the primary endpoint (OS) along with the estimate for median and its 80%, 90% and 95% CI, will be produced using KM method. KM estimates of OS will also be presented graphically at 6, 9 and 12 months.

Same summaries will be produced for all subgroups and other time-to-event endpoints.

7.7.1.1 Subgroup Analyses

Subgroup analysis is planned for the primary endpoint OS to investigate whether treatment effect is consistent within the subgroups. Forest plots will be used to graphically represent the subgroup estimates and corresponding confidence intervals. All the subgroups are provided in a separate document attached in section 11 Appendices. Also, subgroup analysis is conditional upon availability of data.

7.7.2 Secondary Efficacy Analyses

To Assess the Effect of IL4-R Status on Overall Survival (OS)

The secondary efficacy assessment will be to assess the effect of IL4-R status on overall survival (OS). The median OS with its 80%, 90% and 95% confidence interval will be estimated using the KM method, with IL4-R status as strata.

Survival rates at 6, 9, and 12 months and their exact 95% CI for the OS along with the estimate for median and its 80%, 90% and 95% CI, will be produced using KM method. KM estimates of OS will also be presented graphically at 6, 9 and 12 months for each IL4-R stratum.

Objective Response Rate (ORR)

Objective Response Rate (ORR) is the proportion of subjects who achieved a complete response (CR) or partial response (PR) (by RANO-based criteria using both 2-dimensional and volumetric assessments and which may include the incorporation of advanced imaging modalities based on availability of data) out of all treated subjects. Use of sub-therapeutic doses of Avastin will also be considered in determination of ORR (and will result in a variant of the ORR being calculated). Objective response rate will be summarized using percentages along with two-sided 80%, 90% and 95% Clopper-Pearson CI at scheduled time points. Subjects with baseline assessments but no post-treatment assessments will be excluded from the ORR analysis. In addition, the number and percent of subjects by response CR or PR will be summarized. All derived efficacy variables will be displayed in a data listing.

Progression Free Survival (PFS)

Progression Free Survival (PFS) is measured as the time from catheter placement to the date of confirmed disease progression or death from any cause, whichever occurs first. For subjects who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the time of the last radiologic assessment demonstrating lack of progression or, if during the follow-up period, the time of last contact indicating lack of progression.

PFS= Date of disease progression/death – Date of catheter placement +1

PFS rates at 6, 9, and 12 months and their exact 95% CI for the PFS along with the estimate for median and its 80%, 90% and 95% CI, will be produced using KM method. All derived efficacy variables will be displayed in a data listing. KM estimates of PFS will also be presented graphically at 6, 9 and 12 months.

7.7.3 Exploratory Endpoints Analyses

Relationship between OS and Tumor Response Assessment

According to RANO-based criteria, a responder is defined by radiographic and clinical criteria. Target lesion radiological response assessment are defined as below:

Two-Dimensional Criteria: (change in bi-dimensional product)

- Complete Response (CR): 100% decrease in Sum of Perpendicular Diameters (SPD);
- Partial Response (PR): ≥ 50% decrease in Sum of Perpendicular Diameters (SPD);
- Progressive Disease (PD): ≥ 25% increase in Sum of Perpendicular Diameters (SPD);
- Stable Disease (SD): Not CR, PR, PD;
- Not Evaluable (NE).

Three-Dimensional Criteria: (estimated volumetric change)

- Complete Response (CR): 100% decrease;
- Partial Response (PR): ≥ 50% decrease;
- Progressive Disease (PD): ≥ 40% increase;
- Stable Disease (SD): < 65% decrease to < 40% increase;
- Not Evaluable (NE).

Best tumor response will be categorized into two groups: subjects having a best response of stable disease or better (i.e., SD, PR, or CR) or subjects having progressive disease (PD).

All response assessment will be summarized by count and percentages at the scheduled visits.

Tumor response data will also be presented in listing.

The subgroup analysis will be based on OS for all the tumor responses from the document attached in appendices section 11.

Overall Survival will be summarized using KM method for the two categories of tumor responses (CR + PR + SD versus PD), based on different RANO-based assessments (using both 2D or 3D measurements). Survival rates at 6, 9, and 12 months and their exact 95% CI for the OS along with the estimate for median and its 80%, 90% and 95% CI, will be produced using KM method for each subgroup.

KM estimates of OS will be also be presented graphically at 6, 9 and 12 months for each tumor response category and for each subgroup.

Assessment of Anti-MDNA55 Antibody (ADA)

The Anti-MDNA55 antibody will be summarized for each individual concentration groups 1.5, 3, 6, 9 ug/mL and total by descriptive statistics including mean, standard deviation (SD), median and range (min & max) at each scheduled timepoint. Individual and mean plasma concentration-time profiles of anti-MDNA antibody will also be plotted. ADA data will be listed for each subject.

Assessment of Neutralizing Antibodies (NAb)

The neutralizing antibody will be summarized for each individual concentration groups 1.5, 3, 6, 9 ug/mL and total by descriptive statistics including mean, standard deviation (SD), median and range (min & max) at each scheduled timepoint. Individual and mean plasma concentration-time profiles of neutralizing antibody will also be plotted.

Assessment of IL4R Status

IL4R results will be summarized according to the categories below by descriptive statistics including mean, standard deviation (SD), median and range (min & max).

- By concentration of MDNA55 administered (1.5, 3, 6, 9 µg/mL) as well as overall
- By low and high total dose of MDNA55 administered (based on median)

7.7.4 Other Efficacy Endpoints Analyses

Duration of response (DOR)

Duration of response (DOR) is defined as the time from first response PR or better until confirmed disease progression (PD) or death among those subjects achieving a complete response (CR) or partial response (PR) to treatment. Responders alive and progression-free at the time of the analysis will be censored at the time of the last radiologic assessment demonstrating lack of progression or, if during the follow-up period, the time of last contact indicating lack of progression.

DOR = Date of event/censoring - Date of first response +1

DOR rates at 6, 9, and 12 months and their exact 95% CI for the DOR along with the estimate for median and its 80%, 90% and 95% CI, will be produced using KM method. All derived efficacy variables will be displayed in a data listing. KM estimates of DOR will also be presented graphically at 6, 9 and 12 months.

DOR analysis will be based on responders in mITT population. Use of sub-therapeutic doses of Avastin will also be considered in determination of DOR (and may result in a variant of the DOR being calculated).

Duration of Clinical Benefit (DOCB)

Duration of Clinical Benefit (DOCB) is defined as the time from first response or disease stabilization until disease progression or death among those subjects achieving a complete response (CR), partial response (PR), or stable disease (SD). Censoring will be performed in a fashion similar to DOR.

DOCB = Date of event/censoring - Date of first response +1

The analysis will be similar to DOR. All derived efficacy variables will be displayed in a data listing. The Kaplan-Meier estimates of DOCB will be shown in a separate graph.

DOCB analysis will be based on responders in mITT population. Use of sub-therapeutic doses of Avastin will also be considered in determination of DOCB (and may result in a variant of the DOCB being calculated).

Time to Tumor Progression (TTP)

TTP is defined as the time between the date of catheter placement and the date of first evidence of disease progression (PD). For subjects who do not experience tumor progression by the time of data cut-off, TTP will be right censored at the date of last adequate disease response assessment.

TTP = Date of event/censoring – Date of catheter placement +1

The analysis will be similar to DOR or DOCB. All derived efficacy variables will be displayed in a data listing. The Kaplan-Meier estimates of TTP will be shown in a separate graph.

The analysis will be based on mITT population. Use of sub-therapeutic doses of Avastin will also be considered in determination of TTP (and may result in a variant of the TTP being calculated).

7.8 Safety Analyses

The following assessments will be used to evaluate the overall safety of MDNA55:

- Adverse events;
- Vital signs;
- Physical examination;
- Neurological examinations;
- Electrocardiogram (ECG);
- Clinical laboratory results;
- KPS;
- Antibody Assessment (serum anti-MDNA55 antibody and neutralizing antibody);
- Relationship of safety to evaluation of immune parameters (ADA and NAb).

All safety analysis will be performed using the safety population. All safety endpoints will be summarized according to the following subgroups:

- Overall;
- Grouped by concentration (1.5, 3, 6, and 9 ug/mL);
- Grouped by volumes of infusion (volume of infusion will have two categories);

7.8.2 Vital Signs

Vital sign measurements will include Pulse (bpm), Respiratory Rate (breaths/min), Weight (kg/lb), Systolic blood pressure (mmHg) and Diastolic blood pressure (mmHg).

Vital signs data will be summarized using descriptive statistics for actual values and changes from baseline. Only subjects with both baseline and post-dose values will be summarized at each schedule visit.

All vital signs data will be provided as a by-subject listing.

7.8.3 Physical examination

Physical examination will be listed for date, visit and examination status (yes/no).

7.8.4 Electrocardiogram (ECG)

Descriptive statistics for the actual values and changes from baseline over time by visit will be summarized for the below ECG parameter:

- QT interval (msec);
- PR interval (msec);
- QRS duration (msec);
- QTc interval (msec);
- Heart rate (bpm).

In case of multiple assessment done on the same date, the latest assessment should be considered for the summarization of the parameters.

ECG overall interpretation and QTc prolongation will be summarized using frequency and percentage for each scheduled visit for safety population.

All ECG values along with the categorical interpretation will be presented in the listings by subject and visit time point.

7.8.5 Clinical Laboratory Results

Laboratory parameters include:

- Hematology: hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, and WBC differential.
- Coagulation: prothrombin time (PT)/PTT/INR (PTT, corrected, if necessary);

- Serum chemistry: AST, ALT, lactate dehydrogenase (LDH), total bilirubin, indirect bilirubin, alkaline phosphatase, total protein, albumin, sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, uric acid, and glucose

- Urinalysis: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite. Microscopy required only to follow-up clinically significant abnormal findings

- Pregnancy: Serum pregnancy tests will be performed at screening and at 30 and 180 days post CED infusion for all women of childbearing potential

Descriptive statistics for the actual values (and/or change from baseline) for the selected hematology, chemistry, coagulation and urinalysis laboratory parameters will be summarized at each scheduled visit. Parameters with categorical values will be summarized by count and percentages.

Listing of all laboratory data with values flagged to indicate the corresponding classifications relative to the laboratory normal ranges (Low, Normal, High).

Coagulation (prothrombin time [PT], partial thromboplastin time [PTT]), international normalized ratio [INR]), urinalysis, and pregnancy test results will also be listed.

7.8.6 Neurological examinations

Neurological examination includes Mental status, Speech/Comprehension, Memory, Motor function., Cranial nerves, Sensory, Reflexes, Seizures, cerebellar signs, pain other than post op pain, other.

A summary of the shifts (baseline vs post-infusion values) for selected qualitative Neurological examination parameter results will be provided. The below classification would be used to compare the baseline with post infusion findings.

- Present

- Absent

- Normal

- Abnormal Not Clinically Significant (Abnormal NCS)

- Abnormal Clinically Significant (Abnormal CS)

- Not Done

7.8.7 Karnofsky Performance Score (KPS)

The KPS ranking runs from 100 to 0, where 100 is "perfect" health and 0 is death. Descriptive statistics along with frequency of scores will be summarized by count and percentages at the scheduled visits.

A summary of the shifts (baseline vs post-infusion values) will be provided.

7.8.8 Antibody / Immunogenicity

To evaluate anti-MDNA55 antibody (ADA), serum collected at screening (baseline) and Days 14, 30, 120, 240/270 and 360/early termination will be used. The development of anti-MDNA55 antibodies will be analysed as a variable at all dose levels (1.5, 3, 6, 9ug/mL).

The population for analysis of anti-MDNA55 antibodies will be the ADA population.

All ADA data will be presented in the listings by subject and visit time point.

Neutralizing antibody (NAb) titers will be assessed in a subset of the ADA population as appropriate and applicable.

All NAb data will be presented in the listings by subject and visit time point.

7.9 Pharmacokinetic Listing

Systemic exposure to MDNA55 is not expected following intra- and peritumoral infusion and circulating MDNA55 has not been detected in previous clinical studies. To continue to evaluate the potential of systemic exposure, plasma collected at screening (baseline), within 1 hour following infusion end time, ~3 hours following completion of infusion and then (after the ~3 hour sample collection) every 6 hours ± 2 hours until 24 hours and at Day 14.

PK data will be presented for the PK population in listing format by subject and sample collection time point.

8. INTERIM ANALYSIS

No formal interim analyses for efficacy have been conducted or are planned.

9. CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

[redacted]

10.REFERENCES

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