2 SYNOPSIS

Name of the Sponsor: Medicenna Therapeutics Inc.	Individual Study Table Referring to part of the dossier Volume Page	*(For national Authority use only)*
Name of the Finished Product: MDNA55		
Name of Active Ingredient: cpIL-4PE		

Title of Study

An Open-Label, Non-Randomized, Multi-Center Phase-2 Study of Convection-Enhanced Delivery (CED) of MDNA55 in Adults with Recurrent or Progressive Glioblastoma

Investigators and Study Centers

Principal/Coordinating Investigators:

The study was initiated at 11 study sites in the United States (US) and one study site in Poland. Of the 11 sites in the US, three sites were inactive as a result of no enrollment.

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*These sites did not enroll any subjects.	

Publications derived from the study:

- Sampson J, Achrol A, Aghi MK et al. MDNA55 survival in recurrent glioblastoma (rGBM) patients expressing the interleukin-4 receptor (IL4R) as compared to a matched synthetic control. ASCO 2020. Journal of Clinical Oncology 2020 38, no. 15_suppl, 2513.
- Sampson J, Achrol AS, Aghi M et al., Combating recurrent glioblastoma with MDNA55, an

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interleukin-¬4 receptor targeted immunotherapy, through MRI-guided convective delivery. Neuro-Oncology. 2019; 21(6), Issue Supplement_6, November 2019, Page vi8.

- Randazzo D, Achrol A, Aghi MK et al. MDNA55: A locally administered IL4 guided toxin as a targeted treatment for recurrent glioblastoma. *Journal of Clinical Oncology* 2019 37:15_suppl, 2039.
- Achrol A, Bexon M, Bankiewicz K et al. Intratumoral Delivery of MDNA55, an Interleukin-4 Receptor Targeted Immunotherapy, by MRI-Guided Convective Delivery for the Treatment of Recurrent Glioblastoma. *Neuro-Oncology*, Volume 20, Issue suppl_6, 01 November 2018, Pages vi1–vi2.
- Bexon MF, Achrol A, Bankiewicz K et al. Understanding biological activity, tumor response and pseudoprogression in a phase-IIb study of MDNA55 in adults with recurrent or progressive glioblastoma (GB). Annals of Oncology, October 2018, Volume 29, Supplement 8, Pages viii124–viii125.
- Ellingson BM, Merchant F, Merchant R, et al. Validation of modified response assessment in neuro oncology (mRANO) determined PFS as a strong predictor of overall survival in recurrent glioblastoma treated with a targeted immunotoxin. Abstract #: NIMG-28 submitted for SNO 2020 conference.
- Sampson J, Achrol A, Aghi MK et al. Clinical efficacy of MDNA55, an interleukin--4 receptor targeted immunotherapy, in recurrent GBM delivered by convection enhanced delivery (CED). Abstract #: CTIM-13 SNO 2020 conference.
- Ellingson BM, et al. Modified RANO (mRANO), iRANO, and standard RANO evaluation of radiographic response to convection-enhanced delivery of IL4R-targeted immunotoxin MDNA55 in recurrent glioblastoma. Not yet accepted for publication.
- Sampson J, Achrol A, Aghi MK et al. MDNA55, a Locally Administered IL4 Guided Toxin for Targeted Treatment of Recurrent Glioblastoma Shows Long Term Survival Benefit. Abstract # 99LBA ENA 2020 EORTC NCI AACR 32nd symposium.

Study Period	**Phase of Development:** 2
First subject first visit: 23 Mar 2017 **Last subject last visit:** 12 Sep 2019	

Introduction

MDNA55 is being developed for the treatment of recurrent/progressive glioblastoma multiforme (rGBM), an aggressive brain tumor characterized by rapid proliferation of undifferentiated cells, extensive infiltration, and a high propensity to recur. Glioblastoma can be classified as primary, or "*de novo*", arising without a known precursor; or secondary, where a low-grade tumor transforms over time into GBM. Target population for the study was subjects with recurrent primary GBM with no known mutation in isocitrate dehydrogenase (IDH) and who were not indicated for surgical resection at relapse.

Survival in patients with primary GBM is poor; it is a rapidly progressing and universally fatal cancer.

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Survival rates from diagnosis are 40.2% (1-year), 17.4% (2-year), 5.6% (5-year), and 2.8% (10-year), making it one of the most lethal among all cancers. Glioblastoma does not typically metastasize outside of the central nervous system and death usually results due to increased intracranial pressure and herniation caused by uncontrolled growth of tumor within the bone-encased brain cavity. Glioblastoma is considered a rare tumor type, with annual incidence rate for primary GBM of 3.23 per 100,000 persons in the US.

Using current treatment paradigms, most primary GBM patients experience tumor recurrence/progression after standard first line treatment. Treatment options for patients with recurrent primary GBM are very limited and the outcome is generally poor, producing toxicity without benefit. This is mainly due to the lack of tissue specificity with resultant toxicity to normal tissues and consequently, a narrow therapeutic index.

A large percentage of GBMs and their immunosuppressive tumor microenvironment (TME) express the interleukin-4 receptor (IL4R) in relatively high amounts, making it a relevant target for MDNA55.

MDNA55 is a recombinant fusion protein, comprised of an engineered circularly permuted interleukin-4 (cpIL4), fused to a truncated and tailored sequence based on the overall much larger sequence of *Pseudomonas aeruginosa* exotoxin A (PE). Once the fusion protein is bound to the IL4R, it is then endocytosed, and the tailored sequence is cleaved by furin-like proteases. A portion of the tailored sequence containing the adenosine diphosphate (ADP)-ribosylating catalytic domain, is then transported via an intracellular sorting receptor from the transreticular Golgi apparatus to the endoplasmic reticulum and translocated to the cell cytosol. Here, it induces cell death via ADP ribosylation of Elongation Factor-2 (EF-2) and induction of apoptosis through caspase activation.

Intra-tumoral and peritumoral infusion minimizes systemic exposure to the fusion protein, while the image guided convection enhanced delivery (CED) technique enhances exposure of active drug throughout the target region.

MDNA55 has been granted orphan drug status by the US Food and Drug Administration (USFDA) and the European Medicines Agency for the treatment of astrocytic glioma and Fast Track designation for the treatment of rGBM by the USFDA.

Study Objectives

This study was designed to test the hypothesis that median overall survival (mOS) is improved to a clinically significant degree with MDNA55 administered via CED, as compared to current available treatments for rGBM. The design was based on a null hypothesis that mOS was 8 months (based on a clinically weighted average of published studies of FDA-approved therapies) versus an alternative hypothesis of 11.5 months following MDNA55 treatment.

Primary Objective:

- To assess overall survival (OS)

Secondary Objectives:

- To assess the effect of IL4R status on OS;

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- 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;
- To assess progression-free survival (PFS).

Exploratory Objectives:

- To assess the pharmacokinetics (PK) of MDNA55 in peripheral plasma;
- To assess serum anti-MDNA55 antibody (ADA) titers and, if elevated, determine neutralizing antibody (NAb) 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 analysis 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 magnetic resonance imaging (MRI) monitoring.

Methodology

This was a single-arm, non-randomized, open-label, multicenter study, in subjects with primary (*de novo*) GBM without isocitrate dehydrogenase-1 (*IDH1)/* isocitrate dehydrogenase-2 (*IDH2*) mutation, that had recurred or progressed (first or second relapse per RANO criteria) and not indicated for resection at relapse.

Following informed consent and disease/treatment history and eligibility confirmation, all eligible subjects received a single treatment entailing stereotactic surgery associated with placement of one to four catheters followed by an intra- and peritumoral infusion of MDNA55 via convection-enhanced delivery (CED) procedure. All sites were required to use the Brainlab iPlan® Flow planning software (version 3.0.6), Brainlab stepped designed catheters and VarioGuide™ frameless image-guided stereotactic system to generate a pre-treatment plan for placement of catheters according to specified placement guidelines and executing catheter placement. Co-infusion of a contrast agent (gadolinium diethylenetriamine pentaacetic acid [Gd-DTPA], Magnevist®) was applied to assess infusate distribution as well as determine suitability of the iPlan software, Varioguide, Brainlab catheter and catheter placement guidelines to deliver MDNA55.

Infusion via each catheter was initiated at a rate of 3 µL/min/catheter and gradually increased in a stepwise manner to maximum flow rate of up to 50 µL/min/catheter according to Protocol Versions 1.0 to 4.0. In Protocol Versions 1.0 and 2.0, six subjects each received 1.5 µg/mL MDNA55 at an infusion volume of up to 60 mL administered via two catheters (<2 cm tumor) or four catheters (2-4 cm tumor).

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Twelve (12) subjects in Protocol Version 3.0 received 3 µg/mL MDNA55 and three subjects in Protocol Version 4.0 received 1.5 to 3 µg/mL MDNA55 administered via four catheters. Total dose administered was 180 µg.

In Protocol Version 5.0, nineteen (19) subjects received single infusion of 6 to 9 µg/mL MDNA55 at an infusion volume of up to 40 mL administered via four catheters (minimum two catheters). Flow rate was adjusted at the discretion of the Investigator during real time MRI (with subject maintained under anesthesia) provided that it did not exceed 10 µL/min/catheter and such that the duration of infusion lasted up to 48 hours (maximum). After the real-time MRI infusion monitoring period was completed (approximately 1 hour), remainder of the infusion continued with the subject awake and without MRI monitoring. On Day 1 or Day 2 (depending on duration of infusion), MRI was performed within 4 hours of completion of infusion as a final evaluation of MDNA55 infusate distribution. No subjects were enrolled under Protocol Versions 6.0 and 6.1.

MDNA55 was infused with the objective of achieving maximum coverage of the tumor and the peritumoral margin, indicated by distribution of a co-infused contrast agent, gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA, Magnevist®), as observed by MRI. Total dose administered in the study did not exceed 240 µg (the established maximum tolerated dose [MTD] of MDNA55).

Post-treatment follow-up assessment of safety was performed 14 (±3) days after treatment. Thereafter, safety and efficacy assessments were performed at 30, 60, 90 (not evaluated for Protocol Versions 1.0 and 2.0), and 120 (±7) days after treatment and approximately every 8 weeks thereafter until 360 days of active follow-up was completed.

Retrospective analysis of IL4R expression using archived tumor tissue from initial GBM diagnosis and/or tumor tissue sample collected at recurrence was conducted using a validated immunohistochemistry-based assay at a Clinical Laboratory Improvement Amendments (CLIA)-compliant reference laboratory.

Subjects who completed Day 360 assessment without progressive disease (PD) or discontinued early without PD continued to be followed for disease status until progression, where possible. After progression (on study or during post-study follow up), subjects continued to be followed where possible, for survival until death (or termination of data collection by the Sponsor or withdrawal of consent by the subject).

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Number of Subjects

Forty-seven subjects were enrolled in this study; 46 subjects received treatment (one subject underwent catheter placement but discontinued the study before receiving any treatment).

Analysis populations were defined as follows: Intent-to-treat (ITT) and Safety populations were identical and included 47 (100%) subjects; 44 subjects were included in the Per Protocol (PP) population; 43 subjects were included in the Modified Intent-to-treat (mITT) population and; 42 subjects were included in the IL4R population.

Of the 47 subjects enrolled, 8 (17.0%) subjects completed the study and the remaining 39 (83.0%) subjects were discontinued early from the study. Most common reason for early discontinuation was PD as observed in 31 (79.5%) subjects.

The censor date for survival data in this report was 31 Oct 2019 and as of this date, 11 subjects were alive and continued to be followed for survival.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Eligible subjects included male and female subjects, ≥18 years of age with histologically proven primary GBM that had recurred or progressed (first or second recurrence, per standard RANO criteria) after treatment(s), including standard first line surgery and radiotherapy with or without temozolomide and following discontinuation of any previous standard or investigational lines of therapy.

Key inclusion criteria: Subjects had to have a life expectancy >12 weeks and a Karnofsky Performance Status (KPS) ≥70. Subjects had to have a tumor with diameter of ≥1 cm × ≥1 cm (minimum) to 4 cm (maximum) in any direction and no features that made the tumor a poor target for CED (e.g., significant liquefaction or geometric features not conducive to CED) by pre-interventional MRI within 14 days of planned treatment. Subjects had to have adequate bone marrow, liver, and kidney functions. Archived tissue from the time of initial diagnosis was required for retrospective analysis of IL4R status.

Key exclusion criteria: Subjects who were not indicated for tumor resection at eligible relapse and could not have received treatment with prior cytotoxic chemotherapy, immunotherapy, bevacizumab, brachytherapy, Optune, or Gliadel® within specific intervals prior to the planned MDNA55 infusion. Subjects on steroids had to be on a stable or decreasing dose for at least five days prior to imaging. Subjects could not have tumors in the brainstem, multifocal or multicentric satellite tumors, or a tumor with a mass effect. Subjects with known mutations in either the *IDH1* or *IDH2* gene or history of allergy to gadolinium contrast agent were also excluded.

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Test Product, Dose, Mode of Administration, Batch Number

Subjects received a single treatment with MDNA55 at concentrations ranging from 1.5 to 9.0 µg/mL and volumes ranging from 12 to 66 mL (total dose between 18 to 240 µg). Information on the number of subjects who received these doses during each protocol version are provided above in Methodology section above.

The test product (MDNA55) was diluted in Elliotts B® solution to produce an infusate consisting of 0.02% human serum albumin (HSA) and 7 mmoL Gd-DTPA (Magnevist®) (for subjects treated under Protocol Versions 1.0, 2.0 and 3.0) or 2 mmoL Gd-DTPA (for subjects treated under Protocol Versions 4.0 and 5.0). This MDNA55 infusate was administered via infusion using CED with precision planning and real-time MRI monitoring of infusate distribution.

Batch Number: 1-FIN-2516; Manufacture Date: 14 Mar 2016

Reference Therapy, Dose, Mode of Administration, Batch Number

Not applicable

Duration of Treatment

Subjects received a single treatment of MDNA55 infusate via CED infusion, with the infusion flow rate adjusted such that the duration of infusion would be up to 48 hours.

The expected duration of study participation for each subject was up to 12.5 months, including up to 14 days of screening, up to 3-day planning period and a 12-month follow-up period relative to the day of catheter placement/start of infusion being designated as Day 0.

Criteria for Evaluation

Efficacy Endpoints

Primary Endpoint:

- OS, defined as the time from treatment until death.

Secondary Endpoints:

- OS by tumor IL4R status, which was determined based on the 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 Tumor Response Assessment Maps [TRAMs], conditional upon advanced imaging data being available);
- PFS, defined as the time from treatment until PD or death.

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Other Efficacy Endpoints

- Tumor control rate (TCR), defined as the proportion of subjects with the best overall response determined as complete response (CR), partial response (PR), or stable disease, based on different sets of imaging-based response criteria. Use of low dose bevacizumab (Avastin®) was also to be considered in determination of TCR (and could result in a variant of the TCR being calculated);
- Duration of response (DOR), defined as the time from first response until PD or death in subjects with CR or PR to treatment;
- Duration of clinical benefit (DOCB), defined as the time from first response or disease stabilization until PD or death in subjects with CR, PR, or stable disease;
- Time to Tumor Progression (TTP), defined as the time from treatment until tumor progression; did not include death.

Safety Endpoint

- Overall safety of MDNA55, based on assessment of adverse events (AEs [post catheter placement]) including serious adverse events (SAEs), vital signs, physical and neurological examination, electrocardiogram (ECG), clinical laboratory results, and KPS.

Exploratory Endpoints

- Relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and tumor response category using different sets of imaging-based response criteria;
- Relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP, TCR) and IL4R expression status;
- Relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and various prognostic factors (i.e., age, sex, KPS, O6-methylguanine-methyltransferase [MGMT] status, etc.);
- Relationship between efficacy endpoints (i.e., OS, PFS, DOR, DOCB, TTP) and use of concomitant medication (i.e., bevacizumab, steroids);
- 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.);
- Assess performance of the Brainlab catheter during infusion through real-time MRI monitoring.

Other Endpoints

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

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Statistical Methods

All statistical evaluations were performed by Quartesian LLC, using SAS® Version 9.3 or above (SAS® Institute, Cary, North Carolina).

Study Populations

Intent-to-Treat and Safety: ITT and Safety populations were identical and consisted of all subjects who signed an informed consent form and received any amount of study drug.

Modified Intent-to-Treat Population (mITT): mITT population was used for secondary response analyses and consisted of all subjects who received any amount of study drug, had adequate imaging (at least 1 post-treatment scan), and had sufficient clinical data for ORR analysis.

Per-Protocol Population: PP population consisted of all subjects in the mITT Population who had no major protocol violation during the study. Efficacy analyses were conducted on this population in support of the primary efficacy results.

IL4R Population: IL4R population included those who had archived tissue available for analysis of IL4R expression status.

Pharmacokinetic (PK) Population: PK population included those subjects who received any dose of MDNA55 and had at least one post-treatment PK sample available for analysis.

Anti-Drug-Antibody (ADA) Population: ADA population included all subjects who received any dose of study drug and had a pre-treatment baseline blood sample and at least one post-treatment blood sample available for determination of ADA. Neutralizing antibody (NAb) titers were assessed in the ADA population as appropriate and applicable.

Demographic and Baseline Characteristics

Descriptive statistics were provided for subject demographics and disposition, safety, and exposure data and included mean, standard deviation (SD), median, and range for continuous variables and number and percent for categorical variables; 95% confidence intervals (CI) were presented where appropriate.

Efficacy Analyses

Primary Endpoint Analysis

Co-primary endpoint of survival rates at 6 months (OS-6), 9 months (OS-9), and 12 months (OS-12) and their exact 95% CI for the primary endpoint (OS) along with the estimate for median and its 80%, 90%, and 95% CI, were summarized and graphically presented using the Kaplan-Meier (KM) method.

Forest plots were used to graphically represent subgroup estimates and corresponding CIs. The same summaries were produced for all subgroups and for other time-to-event endpoints.

Secondary Endpoints Analyses

Secondary analysis of the primary variable OS was conducted according to IL4R status using the same estimates. Kaplan-Meier (KM) estimates were presented graphically for each IL4R stratum.

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Objective Response Rate (number and percentage of subjects with CR or PR) results were summarized. Radiologic-only data as well as radiologic with clinical data (such as steroid and/or low-dose bevacizumab use and KPS) were used to assess response. Furthermore, response using both local site and an independent central image review was to be evaluated. ORR was summarized using percentages along with two-sided 80%, 90%, and 95% Clopper-Pearson CI.

Progression-Free Survival (PFS) rate at 6 months (PFS-6), 9 months (PFS-9), and 12 months (PFS-12) and their exact 95% CI along with the estimate for median and its 80%, 90% and 95% CIs, were summarized and graphically presented using the KM method.

RANO-based Analyses:

Standard RANO assessment is the currently accepted criteria employed by the USFDA and based on which a response analysis was performed. However, pseudoprogression (PsP) is frequently observed after treatment with immunotherapies such as MDNA55; PsP in these cases confounds the assessment of underlying tumor responses. Thus, it was important to also conduct response assessments based on other derivations of the RANO criteria (i.e., modified RANO [mRANO] applying both two-dimensional (2D) and three-dimensional (3D) tumor measurements and immunotherapy RANO [iRANO]).

Notably, mRANO criteria allowed for continuation of therapy despite initial evidence of radiographic progression. The goal of continuation of this therapy under mRANO criteria was to confirm subsequent tumor growth (true progression) or regression and to rule out possible PsP. It also allowed use of initial radiological scan documenting PsP-related "progression" as a new reference baseline scan to objectively define and document possible PsP events.

The iRANO criteria was also used for response assessment although considered to be less applicable to this study population, due to the requirements of a 6-month observation window that may be too long for patients with rGBM to achieve. Response assessments using 3D volumetric measures are considered exploratory by the FDA. Thus, while all RANO-based analyses were performed, only standard RANO and mRANO (2D) analyses are discussed in this report while iRANO and mRANO (3D) supportive analyses are provided in Section 14 and Section 16 at the end of the main body of this clinical study report (CSR).

Exploratory Endpoints Analyses

The relationship of both OS and PFS with tumor control was explored and analyzed. Overall survival and PFS were summarized using the same estimates as primary or secondary efficacy endpoints for two categories of tumor control (stable disease or better versus PD). All response and tumor control ("tumor response") assessments were summarized by count and percentages at the scheduled visits. Tumor response data were also listed.

Subgroup analyses were conducted on OS and PFS for various prognostic (such as MGMT methylation status) and treatment parameters (such as steroid use). Forest plots were used to graphically represent subgroup estimates and corresponding CIs.

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All derived variables (DOR, DOCB, and TTP) were listed and summarized and the respective KM estimates were graphically presented. Descriptive statistics were used to summarize all the exploratory analyses.

Drug distribution parameters and tumor coverage were based on the safety population; additional information is provided in listings.

Pharmacokinetic Analyses

A by-subject listing by sample collection time point to determine systemic exposure of MDNA55 was generated for the PK population.

Safety Analyses

Adverse events were coded to System Organ Class (SOC) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA)® coding system, Version 22.0 and World Health Organization (WHODRUG) dictionary, Version March 2016. All AEs were collected from the time of catheter placement (thus, deemed to be treatment-emergent) through to end of study visit; all AEs and SAEs were followed until resolution, stabilization, data cut-off, or death. Incidence rates for AEs were summarized according to MedDRA by SOC and/or PT, severity (based on Common Terminology Criteria for Adverse Events [CTCAE] grades Version 5.0), type of event, and relation to study treatment.

Data were summarized using descriptive statistics for actual values and change from baseline at each scheduled visit for clinical laboratory, vital signs, ECG, and KPS. Physical examination data were listed. Change from baseline was provided for KPS and qualitative neurological examination parameters.

A by-subject listing by visit timepoint was generated for all ADA and NAb data.

IL4R Analysis

A retrospective analysis of IL4R expression using archived tumor tissue from initial GBM diagnosis was conducted using a validated immunohistochemistry (IHC)-based assay performed at CLIA-compliant reference laboratory. This rationale was to determine whether there was a correlation between IL4R expression and survival outcomes following MDNA55 treatment. Samples were scored for IL4Rα expression by a board-certified pathologist using the H-Score method with scores ranging from 0 to 300. Based on a positivity cut-off of H-score >60, two subpopulations were identified: IL4R High subjects had H-score >60 and IL4R Low subjects had H-score ≤60.

Summary – Conclusions

Demographic and Baseline Disease Characteristic Results:

In the ITT population, median age of subjects was 56 years (range: 34 to 78 years). Thirty (63.8%) male and 17 (36.2%) female subjects were enrolled with majority of the subjects being White (41 [87.2%]).

Baseline disease characteristics in the ITT population were consistent with study eligibility criteria. Median time between initial diagnosis and start of MDNA55 treatment was 12.72 months (range: 5.15

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to 44.23 months); overall mean maximal tumor diameter at baseline was 3.16 cm and mean tumor volume at baseline was 10.54 cm^3. All 47 (100.0%) subjects underwent prior surgery at initial diagnosis and were not suitable for tumor resection at eligible relapse (i.e., first or second relapse). All but one subject (98%) received prior temozolomide treatment and all but one subject (98%) received prior radiotherapy. Thirteen (27.7%) subjects had relapsed following failure on an alternate investigational therapy prior to enrollment. Approximately half (49.0% subjects) were in lower KPS group (70 or 80). Thirty-seven (78.7%) subjects had one relapse and 10 (21.3%) subjects had two relapses at the time of enrollment.

A review of medical and oncologic history showed 18 of 47 subjects (38.3%) had a history of seizures.

Based on the retrospective IL4R analysis (using archived tumor tissue from initial GBM diagnosis), 23 of 47 subjects (48.9%) showed an H-score >60 (i.e., high expression) and 19 of 47 (40.4%) subjects showed an H-score ≤60 (i.e., low expression) with five unknowns due to unavailability of tumor tissue. With respect to dose, subjects who received a total dose of ≥180 µg (median) of MDNA55 were categorized as the high dose group whereas those who received a total dose of <180 µg MDNA55 were categorized as low dose group. Within the ITT population, 21 subjects were in low dose group and 25 subjects in high dose group.

Based on IL4R status and MDNA55 dose, a subpopulation comprising of IL4R High (receiving any dose) plus IL4R Low subjects receiving high dose (IL4R $Low^{High\ Dose}$) was further analyzed to test the effects on survival.

Baseline characteristics in the PP population were similar to the ITT population. Disease characteristics were also similar between the subgroups when analyzed according to total median dose (<180 µg versus ≥180 µg) and IL4R status (IL4R High versus IL4R Low) and consistent with results in the ITT population.

Protocol Deviations:

Major protocol deviations were reported in 11 (23.4%) subjects. Among these subjects, treatment administration procedure noncompliance occurred in one subject, eligibility criteria deviation occurred in three subjects, and other procedure non-compliance occurred in seven subjects.

Of the three subjects with eligibility criteria deviation, one subject was retrospectively determined to have an eligibility criteria deviation (resulting from inadvertent miscalculation in absolute lymphocyte count) for which exclusion of subject from PP population was not considered warranted. One subject with first-line treatment inconsistent with the Stupp regimen and another subject who was not a good candidate for CED based on screening imaging and subsequent peer review were approved for enrollment in study based on Sponsor/Medical Monitor review but excluded from the PP population. Another seven subjects with other procedure non-compliance did not affect the delivery of the intended dose of study drug at the tumor site and hence were not considered relevant for exclusion from the PP population.

Efficacy Results:

Primary Endpoint

Primary endpoint analysis was based on the ITT population. The null hypothesis was a mOS of 8.0 months (derived from a clinically weighted average of published studies of FDA-approved therapies) versus the alternative hypothesis of 11.5 months mOS, if MDNA55 has beneficial effect.

Following MDNA55 treatment, mOS of the ITT population was 10.2 months with a corresponding 80% one-sided CI of (8.39, 12.75). As the lower bound of the CI did not include 8.0 months, the null hypothesis can be rejected at a one-sided 10% significance level and therefore the primary endpoint for this study was met. For the ITT population, the interval OS rates (co-primary endpoint) were 77% (95% CI: 62%, 86%) at 6 months, 55% (95% CI: 39%, 68%) at 9 months, and 43% (95% CI: 29%, 57%) at 12 months.

In support of the primary efficacy analysis, evaluation of primary endpoint was also conducted on the PP population where mOS was 11.64 months with a corresponding 80% one-sided CI of (8.62, 15.02). As the lower bound of the 80% CI did not include 8.0 months, the null hypothesis can be rejected at a one-sided 10% significance level and therefore the primary endpoint was also met in the PP population. For the PP population, the interval OS rates were 80% (95% CI: 64%, 89%) at 6 months, 56% (95% CI: 40%, 69%) at 9 months, and 46% (95% CI: 31%, 60%) at 12 months.

Subgroup Analysis - Overall Survival:

Exploratory subgroup analyses were conducted on OS in the PP population for various prognostic and treatment parameters. Results are tabulated and subgroups of interest are discussed below.

- Although there was a numerical pattern for longer survival in subjects receiving lower steroid doses than high steroid doses (mOS: 12.75 months versus 8.92 months, respectively), it did not appear to affect MDNA55 activity significantly (p=0.350).
- No significant difference was observed in OS between subjects with KPS (90, 100) versus KPS (70, 80) [mOS: 12.03 months versus 8.92 months, respectively; p=0.456].
- No significant difference was observed in OS between subjects with unmethylated and methylated MGMT status (mOS: 10.20 months versus 11.64 months, respectively; p=0.632).
- Effect of MDNA55 dose based on median (180 µg) showed no significant difference between subjects receiving low dose (<180 µg) versus those receiving high dose (≥180 µg) [mOS: 11.64 months versus 15.15 months; p=0.670]. Interestingly, a dose-effect relationship on survival was seen when further examined together with IL4R expression (discussed below under secondary endpoints).

Overall Survival – Subgroup Analysis (PP Population)

Subgroup	Categories	mOS (95% CI) in months from start of treatment	OS-12	p-value; HR (95% CI)
IL4R status	IL4R Low*	8.39 (5.67, 12.75)	33%	0.215; 0.62 (0.29, 1.33)
	IL4R High*	15.02 (7.70, 16.43)	57%	
IL4R status and MDNA55 dose	IL4R High + IL4R $Low^{High\ Dose}$	15.02 (7.70, 16.43)	55%	0.005; 0.30 (0.13, 0.73)
	IL4R $Low^{Low\ Dose}$	8.00 (0.82, 11.64);	13%	
Gender	Males	11.64 (7.70, 16.43)	ND	0.972; 1.01 (0.50, 2.06)
	Females	10.20 (6.00, 15.87)	ND	

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Age	<56 years	12.03 (8.62, 16.43)	ND	0.571; 1.22 (0.61, 2.43)
	≥56 years	8.38 (6.00, 16.46)	ND	
Baseline KPS scores	70 or 80	8.92 (5.90, 16.43)	39%	0.456; 0.77 (0.39, 1.53)
	90 or 100	12.03 (8.36, 21.48)	54%	
MGMT status	Methylated	11.64 (5.74, 16.43)	41%	0.632; 0.84 (0.41, 1.71)
	Unmethylated	10.20 (8.36, 15.15)	46%	
Total dose administered	Low (<180 µg)	11.64 (7.48, 15.02)	43%	0.670, 0.86 (0.42, 1.75)
	High (≥180 µg)	15.15 (7.70, 21.48)	51%	
Overall bevacizumab exposure	No	8.39 (5.90, 21.48)	41%	0.423; 1.33 (0.66, 2.68)
	Yes	15.02 (8.62, 16.43)	52%	
On-study bevacizumab exposure (6 µg/mL and 9 µg/mL cohorts only)	Yes	15.15 (3.05, NE)	67%	0.224; 2.42 (0.56, 10.44)
	No	7.33 (4.39, NE)	NE	
Steroid use (1 week prior to treatment and 30 days after treatment)	<178 mg	12.75 (8.36, 16.46)	52%	0.350; 1.39 (0.69, 2.81)
	≥178 mg	8.92 (6.03, 15.15)	38%	
Steroid use (within 2 weeks after start of treatment)	<95.3 mg	9.64 (7.64, 15.87)	ND	0.882; 0.95 (0.47, 1.90)
	≥95.3 mg	11.77 (6.46, 21.48)	ND	
Clinical site enrollment	>4 subjects	11.77 (7.90, 15.15)	ND	0.482; 1.38 (0.56, 3.41)
	≤4 subjects	8.39 (2.43, NE)	ND	

Abbreviations: CI = confidence interval, HR = hazard ratio, KPS = Karnofsky Performance Status, OS-12 = overall survival rate at 12 months, MGMT = O6-methylguanine-methyltransferase, mOS = median overall survival, ND = not determined, NE = not evaluable (i.e., very limited data for this data point), PP = per protocol.

*OS based on IL4R expression status was secondary endpoint and is described below.

Note: p-values and HRs with corresponding 95% CIs were generated for subgroup analysis to further assess and compare the effect of MDNA55 between the subgroups; p-value was based on the unstratified log rank test (calculated by comparing lower cell versus upper cell in this table for each category).

HR was based on Cox proportional hazards model for OS with factor as each variable tested (calculated by comparing lower cell versus upper cell in this table for each category).

Secondary Endpoints

Overall Survival by Tumor IL4R Status

When stratified based on IL4R expression, a substantial numerical difference was observed for improved survival in IL4R High subjects when compared with IL4R Low subjects, which approached but did not achieve significance due to limited sample size.

Kaplan-Meier Estimate for Overall Survival by IL4R Status (PP Population)		
	IL4R High (N = 21)	**IL4R Low (N = 19)**
mOS (95% CI) in months	15.02 (7.70, 16.43)	8.39 (5.67, 12.75)
OS-6, OS-9, and OS-12	86%, 62%, and 57%	68%, 46%, and 33%
p-value Hazard ratio (95% CI)	0.215 0.62 (0.29, 1.33)	
Abbreviations: CI = confidence interval; IL4R = interleukin 4 receptor; mOS = median overall survival; OS-6, OS-9, and OS-12 = overall survival rates at 6, 9, and 12 months.		

Kaplan-Meier estimates of OS by IL4R subgroups and MDNA55 dose are summarized in table below. Overall, pooled population of IL4R High + IL4R Low $^{\text{High Dose}}$ showed significantly improved OS in comparison to subjects in IL4R Low$^{\text{Low Dose}}$ group (mOS: 15.02 months versus 8.0 months and OS-12: 55% versus 13%, respectively; p=0.005). These data suggest that MDNA55 has the potential to benefit all rGBM subjects treated at the high dose (≥180 µg) irrespective of IL4R expression.

Comparison of Kaplan-Meier Estimates of Overall Survival by IL4R Group and MDNA55 Dose (PP Population)				
IL4R Groups and MDNA55 Dose	**N**	**Median OS (95% CI)**	**OS-12**	**p-value[a] HR (95% CI)[b]**
IL4R Low$^{\text{Low Dose}}$	8	8.00 (0.82, 11.64)	13%	0.055 0.35 (0.11, 1.07)
IL4R Low$^{\text{High Dose}}$	11	NE (4.39, NE)	53%	
IL4R High$^{\text{Low Dose}}$	12	13.52 (6.00, 23.38)	58%	0.009 0.25 (0.08, 0.76)
IL4R Low$^{\text{Low Dose}}$	8	8.00 (0.82, 11.64)	13%	
IL4R High$^{\text{Low Dose}}$	12	13.52 (6.00, 23.38)	58%	0.561 1.34 (0.49, 3.65)
IL4R High$^{\text{High Dose}}$	9	15.15 (5.74, NE)	56%	
IL4R High$^{\text{High Dose}}$	9	15.15 (5.74, NE)	56%	0.697 0.79 (0.25, 2.54)
IL4R Low$^{\text{High Dose}}$	11	NE (4.39, NE)	53%	
IL4R High + IL4R Low$^{\text{High Dose}}$	32	15.02 (7.70, 16.43)	55%	0.005 0.30 (0.13, 0.73)
IL4R Low$^{\text{Low Dose}}$	8	8.00 (0.82, 11.64)	13%	
Abbreviations: CI = confidence interval, HR = hazard ratio, IL4R = interleukin 4 receptor, N = sample size, NE = not evaluable (i.e., very limited data for this data point), OS-12 = overall survival at 12 months, PP = per protocol population. Overall survival (OS) was defined as time from catheter placement until death from any cause. OS = Date of death/censored - Date of catheter placement + 1. Median survival rate and associated confidence intervals (CI) were calculated using Proc Lifetest, KM Method, in SAS. [a] p-value was based on the unstratified log rank test (calculated by comparing upper cell versus lower cell in this table for each category in IL4R group and MDNA55 dose column).				

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[b] Hazard ratio was based on Cox proportional hazards model for OS with factor IL4R dose receiving group status (calculated by comparing upper cell versus lower cell in this table for each category in IL4R group and MDNA55 dose column).

Objective Response Rate and Progression Free Survival

Pseudoprogression (PsP) is a transient pattern of changes on MRI that often mimics tumor progression; indeed, it is often indistinguishable from early progression on MRI but is not necessarily accompanied by clinical deterioration. In this study, response assessments were performed using different RANO-based criteria to provide a thorough evaluation of MDNA55 treatment effect and to account for PsP.

In data presented below, mRANO, which allows for continuation of therapy despite initial evidence of radiographic progression, was observed to be a better predictor of mOS as well as PFS as compared to standard RANO. This study also included response analysis based on iRANO and analysis based on local radiologic assessments and volumetric assessments (for mRANO) as exploratory components. This report focused on response assessment based on mRANO and standard RANO criteria using centrally-read radiologic-only and radiologic + clinical assessments. The data associated with iRANO and 3D mRANO analyses are provided in Section 14 and Section 16 at the end of the main body of the CSR.

Response assessments were also conducted using radiologic-only and radiologic + clinical assessments (such as steroid and/or low-dose bevacizumab use and KPS) to independently determine, in a blinded manner, the rates of PD due to strictly radiographic changes and those changes that integrate neurological changes or steroid changes that might influence interpretation of the resulting image measurements.

Summaries of ORR and PFS based on an independent central review are presented below.

Objective Response Rate (mITT Population)		
	Standard RANO	**mRANO**
Radiologic Only, n (%)	1/41 (2.4%)	1/41 (2.4%)
Radiologic+Clinical, n (%)	1/38 (2.6%)	1/38 (2.6%)
Abbreviations: mITT = modified intent-to-treat, mRANO = modified response assessment in neuro-oncology criteria, RANO = response assessment in neuro-oncology criteria.		

While few subjects achieved a radiographic response, it is important to highlight the inadequacy of ORR as an endpoint in immunotherapy studies that exhibit a high frequency of PsP. In this study, PsP was observed in 20 of 41 (48.8%) subjects. Although the mRANO criteria does allow for transient worsening prior to therapeutic response, the best response that can be achieved following PsP is stable disease, making it impossible to have both a transient inflammatory response and an objective radiographic response.

Progression Free Survival (mITT Population)	
	Median PFS (95% CI) in months [PFS-6, PFS-9, and PFS-12]

	Standard RANO	mRANO
Radiologic Only	1.15 (0.98, 1.80) [2%, 2%, NE]	3.61 (2.62, 7.70) [33%, 27%, 27%]
Radiologic+Clinical	1.11 (0.98, 1.80) [3%, 3%, NE]	1.93 (1.15, 3.77) [28%, 17%, NE]

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat, mRANO = modified response assessment in neuro-oncology criteria, NE = not evaluable (i.e., very limited data for this data point); PFS-6, PFS-9, and PFS-12 = progression free survival rate at 6, 9, and 12 months; RANO = response assessment in neuro-oncology criteria.

Subgroup Analysis – Progression Free Survival

Exploratory subgroup analyses were conducted to evaluate the effect of the prognostic and treatment parameters on PFS; results of certain parameters are summarized below. Analyses for other subgroups where there was adequate sample size for valid analyses (i.e., age, gender, MGMT status, KPS score, tumor coverage, and steroid use) are presented in detail in the body of this report.

Due to PsP, PFS results using mRANO assessment (summarized below) were considered to be robust.

Subgroup Analysis for Progression Free Survival – Modified RANO Assessment (mITT Population)

Subgroup (Sources)	Categories	Median PFS (95% CI) in months	PFS-6, PFS-9, and PFS-12	p-value; HR (95% CI)
		Radiologic Only Radiologic+Clinical	Radiologic Only Radiologic+Clinical	Radiologic Only Radiologic + Clinical
IL4R Status	IL4R Low	4.62 (1.80, 7.70) 1.80 (0.95, NE)	27%, 13%, and 13% 32%, NE, and NE	0.968; 0.97 (0.40, 2.36)
	IL4R High	2.79 (1.93, NE) 2.95 (1.11, NE)	34%, 34%, and NE 31%, 31%, and NE	0.219; 0.59 (0.25, 1.38)
Total Dose Administered	Low Dose (<180 µg)	2.95 (1.34, NE) 2.95 (1.34, NE)	43%, 43%, and 43% 47%, 31%, and NE	0.811; 1.11 (0.46, 2.69)
	High Dose (≥180 µg)	3.84 (1.84, 7.70) 1.48 (0.95, 3.61)	27%, 18%, and 18% 15%, 7%, and NE	0.051; 2.26 (0.97, 5.25)
IL4R Status and MDNA55 dose	IL4R High + IL4R Low $^{\text{High dose}}$	3.02 (2.62, 7.70) 1.93 (1.11, 3.84)	31%, 24%, and 24% 27%, 20%, and NE	0.460; 1.80 (0.39, 8.42)
	IL4R Low $^{\text{Low dose}}$	NE (1.34, NE) NE (1.34, NE)	NE NE	0.391; 0.42 (0.06, 3.18)
Overall bevacizumab exposure	Not exposed	3.61 (1.80, NE) 3.61 (1.05, NE)	40%, 40%, and 40% 39%, 29%, and NE	0.498; 0.74 (0.31, 1.79)
	Exposed	3.02 (2.62, 5.08) 1.93 (0.98, 3.84)	17%, NE and NE 13%, NE and NE	0.152; 0.54 (0.23, 1.27)

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On-study bevacizumab exposure (6 and 9 µg/mL cohorts only)	Exposed	3.84 (0.82, NE) 0.95 (0.82, 3.84).	20%, 0% and 0% 11%, NE and NE	0.746; 1.25 (0.32, 4.88)
	Not exposed	4.62 (0.92, NE) 1.80 (0.92, NE)	NE NE	0.456; 0.65 (0.20, 2.05)

Abbreviations: CI = confidence interval, HR = hazard ratio, IL4R = interleukin 4 receptor, mITT = modified intent-to-treat, ND = not determined, NE = not evaluable (i.e., very limited data for this data point), PFS = progression free survival.

Note: PFS-6, PFS-9, and PFS-12 equals PFS rate at 6, 9, and 12 months.

Note: p-values and HRs with corresponding 95% CIs were generated for subgroup analysis to further assess and compare the effect of MDNA55 between the subgroups; p-value was based on the unstratified log-rank test and HR was based on Cox proportional hazards model for PFS with factor as each subgroup (calculated by comparing lower cell versus upper cell in this table for each subgroup category)

Other Endpoints

Tumor Control

Percentage of subjects exhibiting tumor control (tumor stabilization or shrinkage) was evaluated to address possible PsP and to further appraise MDNA55 treatment effect. Results are summarized below.

Tumor Control Based on Radiologic Only and Radiologic + Clinical Assessment using RANO and mRANO Criteria (mITT Population)

	Standard RANO	**mRANO**
Radiologic Only, n/N (%)	15/41, 36.6%	31/41, 75.6%
Radiologic + Clinical, n/N (%)	11/38, 28.9%	20/38, 52.6%

Abbreviations: mITT = modified intent-to-treat, mRANO = modified response assessment in neuro-oncology, n = subjects with response; N = subjects analyzed, RANO = response assessment in neuro-oncology.

Duration of Response (DOR)

As assessed by RANO-based criteria, only one subject showed a response of CR (DOR: 229 days, PFS: 358 days).

Duration of Clinical Benefit (DOCB):

Values for median DOCB with corresponding 95% CIs based on independent central review are summarized below.

Duration of Clinical Benefit Based on Radiologic Only and Radiologic + Clinical Assessment using RANO and mRANO Criteria (mITT Population)

	Median DOCB (95% CI) in months	
	Standard RANO	**mRANO**
Radiologic Only	1.18 (0.92, 1.84)	2.95 (1.18, 10.20)

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Radiologic + Clinical	1.11 (0.92, 2.07)	1.90 (0.95, NE)

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat, mRANO = modified response assessment in neuro-oncology criteria, NE = not evaluable (i.e., very limited data for this data point), RANO = response assessment in neuro-oncology criteria.

Time to Tumor Progression

Values for median TTP with corresponding 95% CIs based on independent central review are summarized below.

Time to Tumor Progression (TTP) Based on Radiologic Only and Radiologic + Clinical Assessment using RANO and mRANO Criteria (mITT Population)

	Median TTP (95% CI) in months	
	Standard RANO	**mRANO**
Radiologic Only	1.15 (0.98, 1.80).	3.61 (2.62, 7.70)
Radiologic+Clinical	1.11 (0.98, 1.80)	1.93 (1.15, 3.77).

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat population, mRANO = modified response assessment in neuro-oncology criteria, RANO = response assessment in neuro-oncology criteria.

Exploratory Analyses

Best Response

Waterfall plots depicting best tumor response from baseline and nadir (largest tumor measurement preceding the current scan) were performed for selected groups to supplement evaluation of tumor control (defined as the proportion of subjects with best overall response of CR, PR, or stable disease. Based on independent central review:

- Best response assessed from baseline using standard RANO criteria showed 15 of 41 subjects (37%) displayed tumor control.
- In order to account for initial PsP, the best tumor response was also evaluated using mRANO criteria, which allowed use of initial radiologic progression (nadir) as a new reference scan to account for possible PsP. Overall, 31 of 41 (75.6%) subjects showed tumor control and of these, 20 exhibited tumor control after PsP.
- Best response assessed from nadir in the sub-population consisting of IL4R High + IL4R Low $^{\text{High Dose}}$ subjects using mRANO criteria showed tumor control in 26 of 32 subjects (81.3%) of which 15 subjects exhibited tumor control after PsP.

Correlation of OS and Tumor Control

Results of correlation between tumor control and OS based on independent central review (radiologic only assessment) are summarized below.

Overall Survival by Tumor Control Based on RANO and mRANO (mITT Population)

	Median OS (95% CI) in months [OS-6, OS-9, and OS-12]	
	Standard RANO	**mRANO**
Radiologic Only	15.02 (6.00, 23.97)	15.02 (8.36, 21.48)
	[80%, 66%, 51%]	[87%, 67%, 57%]
p-value [a]	0.561	0.034
Hazard ratio (95% CI) [b]	0.79 (0.37, 1.73)	0.42 (0.19, 0.96)

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat population, mRANO = modified response assessment in neuro-oncology criteria, OS-6, OS-9, and OS-12 = overall survival rate at 6, 9, and 12 months; PD = progressive disease, standard RANO = response assessment in neuro-oncology criteria.

Note: Subjects with PD had median OS of 11.64 months (95% CI: 7.90, 16.46); OS-6, OS-9, and OS-12 was 85%, 58%, and 49%, respectively using standard RANO criteria. Subjects with PD had a median OS of 8.77 months (95% CI: 4.39, 12.75); OS-6, OS-9, and OS-12 was 70%, 40%, and 30%, respectively.

[a] p-value was based on the unstratified log rank test. The p-value in this table indicated the statistical comparison in the survival rates when compared with subjects with progressive disease.

[b] Hazard ratio was based on Cox proportional hazards model for overall survival with factor as Best Tumor Response.

When tumor response was correlated with OS using radiologic-only assessment, subjects showing tumor control based on mRANO criteria demonstrated longer OS than those who had PD (mOS: 15.02 months versus 8.77 months and OS-12: 57% versus 30%, respectively; p = 0.034). However, the improved outcome of OS in subjects with tumor control than in subjects with PD was less pronounced when tumor response was assessed using standard RANO (mOS: 15.02 months versus 11.64 months and OS-12: 51% versus 49% in subjects with PD; p = 0.561). It is important to note that the mOS of 11.6 months and OS-12 of 49% in subjects with PD may include subjects with PsP since standard RANO criteria does not account for PsP cases.

Correlation of PFS and Tumor Control

Results of correlation between tumor control and PFS based on independent central review (radiologic-only assessment) are summarized below.

Progression Free Survival by Tumor Control Based on RANO and mRANO (mITT Population)		
	Median PFS (95% CI) in months [PFS-6, PFS-9, and PFS-12]	
	Standard RANO	**mRANO**
Radiologic Only	2.13 (1.80, 2.79) [7%, 7%, NE]	4.62 (2.95, NE) [40%, 33%, 33%]
p-value [a]	<0.001	<0.001
Hazard ratio (95% CI) [b]	0.00 (0.00, NE)	0.00 (0.00, NE)

Abbreviations: CI = confidence interval, mITT = modified intent-to-treat population, mRANO = modified response assessment in neuro-oncology criteria, NE = not evaluable, PD = progressive disease, PFS-6, PFS-9, and PFS-12 = progression-free survival rate at 6, 9, and 12 months, standard RANO = response assessment in neuro-oncology criteria.

[a] p value was based on the unstratified log rank test. The p-value in this table indicated the statistical comparison in the PFS rates when compared with subjects with PD.

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[b] Hazard ratio was based on Cox proportional hazards model for overall survival with factor as best tumor response.

When tumor response was correlated with PFS using radiologic-only assessment, subjects showing tumor control based on mRANO criteria demonstrated longer PFS than subjects who had PD (mPFS: 4.62 months versus 1.28 months, respectively; $p<0.001$). However, the improved outcome in PFS although significant in subjects with tumor control than in subjects with PD, was less pronounced when tumor response was assessed by standard RANO criteria (mPFS: 2.13 months versus mOS = 0.98 months, respectively; $p<0.001$).

The overall correlation results of OS and PFS with tumor control indicate that response based on PsP provides a more reliable surrogate for survival with immunotherapy agents like MDNA55 and supports published evidence that PsP potentially indicates higher treatment efficacy due to increased infiltration of the tumor site by immune cells or continued tumor growth until a sufficient response develops due to the time required to mount an adaptive immune response. These results are also consistent with earlier reports from MDNA55 studies suggesting that occurrence of immunogenic cell death (cell death resulting in the release of soluble mediators and triggering of an immune response) following treatment with MDNA55 is associated with improved clinical prognosis and survival.

MDNA55 Distribution and Tumor Coverage

Determination of volume of distribution (Vd), based on the assessment of Gd-DTPA distribution, overall median tumor coverage achieved was 52.66% (range: 0 to 97.8%); median tumor coverage including a 1 cm peritumoral margin was 55.14% (range: 5.4% to 95.2%), and median tumor coverage including a 2 cm peritumoral margin was 37.22% (range: 2.2% to 82.9%). Median Vd/Vi ratio was 1.35 (range: 0.1 to 4.8). Evaluation of drug distribution and tumor coverage on survival showed that there was no appreciable difference between groups above and below the median in any of the parameters examined.

Safety:

In general, the safety profile of MDNA55 in this study was consistent with findings from previous clinical studies. No specific patterns were observed for any of the safety observations with respect to concentrations (1.5-9 µg/mL) used in this study within the established MTD of 240 µg. A consistent pattern was observed (in terms of distribution of AEs and SAEs) with majority of the subjects experiencing events related to Nervous System Disorders SOC.

Adverse Events

Overall, 46 (97.9%) subjects experienced a total of 590 AEs with incidence comparable between the MDNA55 concentrations. There were no indications in the pattern of AEs suggesting that the events were associated with any systemic effects of MDNA55. The most common AEs were reported in the Nervous System Disorders SOC, consistent with the disease under study. Seizure, fatigue, headache, and muscular weakness were the most commonly reported AEs (>30% incidence). Majority of AEs (95.7%) occurred during the post-treatment follow-up period.

Relatedness: Of the 46 subjects with AEs, 32 subjects had 139 AEs considered possibly related to study drug and/or CED infusion procedure. Seizure (n = 10), fatigue (n = 9), headache (n = 8), and pyramidal tract syndrome (n = 8) were the most commonly reported possibly related AEs.

Severity: Based on a ≥5% cutoff for incidence of AEs by severity, 19 (40.4%) subjects experienced one or more Grade 3 AEs, 2 (4.3%) subjects experienced one or more Grade 4 (life-threatening) AEs, and 8 (17.0%) subjects had Grade 5 (fatal) AEs during study.

Deaths: As of the study censor date (31 Oct 2019), 36 subjects had recorded death and 11 subjects were alive and continued to be followed up. Of these 36 subjects, most subjects (23 [63.8%]) died due to PD and in 8 (22.2%) subjects, death was the resulting outcome of an AE, most (6 of 8) of which were considered unrelated to study drug and/or CED procedure. These included disease progression (n = 3), cardiac arrest (n = 1), neurological decompensation (n = 1), and septic shock (n = 1). The SAEs of disease progression (n = 3) that had an outcome of death were reported in line with provision in the clinical protocol for reporting of SAEs. Two subjects had Grade 5 events that were considered related to study drug and/or CED procedure which included neurological symptom (n = 1; occurring 71 days after treatment) and cerebral hemorrhage (n = 1; occurring 14 days after treatment). Primary cause of death was reported as unknown in four subjects and cardiac arrest in one subject.

SAEs**:** Twenty-four of 47 subjects (51.1%) experienced SAEs. Of these, 13 subjects (27.7%) had study drug-related SAEs and 12 (25.5%) had SAEs related to CED procedure (Note: one subject experienced a SAE of cerebral hemorrhage which was considered possibly related to study drug and CED procedure; in total number of subjects with SAEs, this subject was counted once). Seizure was the only possibly related SAE reported in at least 5% of subjects (n = 4, 8.5%) during the study. One subject was discontinued before receiving any MDNA55 infusion due to SAE of Grade 3 complication of device insertion.

AEs leading to treatment discontinuation: Two subjects (4.3%) had three events which led to discontinuation of infusion. One subject experienced non-serious AEs of Grade 2 aphasia and Grade 3 hemiparesis, and one subject experienced serious Grade 4 peritumoral edema. All events occurred during MDNA55 infusion and were considered related to study drug and/or CED procedure.

Clinical Laboratory, Vital Signs, and ECG

Clinical Laboratory and Vital Signs: Overall, no specific patterns were observed from baseline overtime in mean changes in clinical laboratory (hematology and serum chemistry) and vital signs parameters through to the end of study. Abnormal clinically significant individual laboratory values reported in at least 5% of subjects as AEs included hypokalemia (n=7), decrease in lymphocyte count (n=5), increase in alanine aminotransferase (n=4), hyperglycemia (n=3), and increase in blood lactate dehydrogenase (n=3).

ECG: Nine subjects had corrected QT using Bazett's equation (QTcB) >450 msec and two subjects each had QTcB >480 msec and QTcB >500 msec at the end of infusion. Three subjects had an increase in QTcB value by >30 msec and two subjects had a change in QTcB by >60 msec. One subject had corrected QT using Fridericia's equation (QTcF) >450 msec. None of the ECG abnormalities were considered clinically significant by the investigator.

KPS Score: In majority of subjects (>80%), KPS scores either remained stable or improved from baseline at all post-treatment follow-up timepoints indicating no deterioration in physical function. In assessment of change from baseline against post infusion follow-up timepoints, KPS score <70 were reported in 7/41 subjects on Day 30, 6/38 subjects on Day 60, 5/25 subjects on Day 90, 3/22 subjects on Day 120, and 2/12 subjects on Day 180. On Day 360, 1/9 subjects had KPS score <70 and 8/9 subjects had KPS ≥70.

Neurological Examination: At baseline (before catheter placement), clinically significant abnormal findings were reported for following parameters: speech/comprehension (n = 4), memory (n = 3), motor function (n = 3), cranial nerves function (n = 4) and sensory function (n = 1). Overall, 15 (31.9%) subjects were on prophylactic anti-epileptic medications prior to catheter placement.

During post-infusion period, majority of subjects had stable neurological functions with no clinically meaningful abnormalities during neurological examination. The abnormal neurological findings

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reported were mostly during the later part of the follow-up period and consistent with underlying PD and neurological AEs that occurred during post-infusion follow-up period.

Pharmacokinetic: Pharmacokinetic results were below LLOQ at all timepoints, suggesting that intact MDNA55 did not enter the systemic circulation in measurable quantities following intracranial infusion.

Immunogenicity: Serum samples for immunogenicity analysis were collected for evaluation of ADAs and NAbs.

- Of the 46 treated subjects, 19 were confirmed to be ADA positive (17 subjects had positive samples post-treatment only and 2 subjects were positive at screening and post-treatment).
- Confirmed positive samples were analyzed for ADA titer. Titers increased by Day 14, peaked by Day 30 and were detectable up to five months in some subjects.

The 19 subjects with confirmed-positive ADA samples were then tested for NAbs: 16 subjects (84.2%) had samples that showed inhibitory effect on MDNA55 cytotoxic activity, indicating presence of NAbs. The degree of inhibition in 16 subjects ranged from 6.2% to 101.3%.

Summary and Conclusions

- A single treatment with MDNA55 met the primary endpoint. Median OS of 10.2 months in the ITT population and 11.6 months in the PP population, versus the null hypothesis of 8.0 months, was achieved in this high-risk patient population.
- Subjects with high IL4R expression status when pooled together with subjects having low IL4R expression status treated with high doses of MDNA55 showed a mOS of 15.0 months with a 12-month survival rate of 55%. Despite being an aggressive form of GBM, MDNA55 displays a likely potential to benefit this patient population in future clinical studies with improved survival outcome when treated at high dose (≥180 µg), irrespective of IL4R expression.
- MDNA55 activity was independent of MGMT methylation status with survival outcomes similar between methylated and unmethylated MGMT population in this study.
- Using standard RANO criteria in assessing tumor control, 37% of all evaluable subjects had disease stabilization or tumor shrinkage with one subject having a durable CR.
- Treatment with MDNA55 triggered PsP in 48.8% of the treated subjects.
- Using standard RANO criteria, PFS does not correlate with survival outcome and therefore does not serve as a useful surrogate outcome measure in future clinical trials of MDNA55. Modified RANO criteria, which accounts for PsP, and contributes to measurement of PFS, showed clinically meaningful results for both mOS and PFS.
- Using mRANO criteria, TCR was 76% in all evaluable subjects. Furthermore, when IL4R patients treated at low doses were excluded from this analysis, the TCR was 81.3%.
- Median PFS based on mRANO criteria was 3.61 months; PFS-6 was 33%, PFS-9 was 27%, and PFS-12 was 27% among the mITT population.
- Survival outcome was similar for subjects with a true response and subjects with initial PsP.
- Overall, the safety profile was consistent with findings from previous clinical studies of MDNA55. No clear, specific, or consistent patterns were observed in the incidence of AEs across the range of MDNA55 dosing or infusion parameters evaluated (i.e., concentrations, total median dose, rate of infusion, volume of infusion and number of catheters used etc.) during study. Drug-related AEs were primarily neurological or an exacerbation of pre-existing neurological conditions due to primary disease of GBM.
- The CED procedure was generally well tolerated with only two subjects discontinuing infusion due to AEs.
- One subject died due to Grade 5 neurological symptom (71 days after treatment) which was considered possibly related to study drug and unrelated to CED procedure and one subject died to cerebral hemorrhage (14 days after treatment), considered possibly related to study drug and CED procedure. In majority of the subjects who died, cause of death was due to eventual PD.
- Pharmacokinetic results were well below the LLOQ at all timepoints, suggesting that intact MDNA55 did not enter the systemic circulation at measurable levels following intracranial infusion.
- Of 19 subjects confirmed positive for ADA during study, 16 subjects tested positive for NAbs where the inhibition of MDNA55 cytotoxic activity ranged between 6.2% to

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101.3%. However, these effects seen in serum may not be representative of effects within the tumor beyond the blood-brain barrier with no clear implications for repeated dosing.

- Overall, the study findings suggest MDNA55 to be a rationally designed IL4R targeted therapy with a potential to meaningfully improve the overall survival with an acceptable risk-benefit profile in a population expected to have poorer prognosis and survival outcome. Advanced drug delivery technique employed in this study provide future opportunities to potentially deliver substantive benefit in patients with rGBM and to explore the efficacy of MDNA55 in a targeted population.

Date of the Report: 05 Mar 2021