Statistical Analysis Plan

Study Title:

A Phase 2, open-label, multicenter study to evaluate the safety and efficacy of repeated administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF cells) in participants with Progressive Multiple Sclerosis (MS)

NCT: NCT03799718

April 12, 2019

STATISTICAL ANALYSIS PLAN

STUDY TITLE:

A Phase 2, Open-Label Multicenter Study to Evaluate the Safety and Efficacy of Repeated Administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF Cells) in Participants with Progressive Multiple Sclerosis (MS)

PROTOCOL NUMBER:

BCT-101-US

PHASE II

FINAL VERSION: 1.0

DATE OF PLAN: April 12, 2019

BASED ON:

Clinical Study Protocol BCT-101-US – Amendment 1

Case Report Forms Ver: [07] 20190313

STUDY DRUG:

MSC-NTF Cells, NurOwn®

SPONSOR:

Brainstorm Cell Therapeutics Ltd.

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
9-HPT	9-Hole Peg Test
AE	Adverse Event
ALP	Alkaline phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine aminotransferase (alanine transaminase)
AST	Aspartate aminotransferase (aspartate transaminase)
ATC	Anatomical Therapeutic Chemical
BA	Bioavailability
BDNF	Brain Derived Neurotrophic Factor
BE	Bioequivalence
BMA	Bone marrow aspiration
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CM	Concomitant Medications
CNS	Central nervous system
CPIW	Center Point Insight Watch from ActiGraph
CRO	Clinical Research Organization
CSF	Cerebrospinal Fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EE	Efficacy Evaluable Analysis Set
EMG	Electromyography
ET	Early Termination
FS	Functional System
FDA	Food and Drug Administration
FVC	Forced Vital Capacity

Abbreviation	Term
GDNF	Glial Derived Neurotrophic Factor
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGF	Hepatocyte Growth Factor
HIV	Human immunodeficiency virus
hMSCs	Human Mesenchymal Stem Cells
Ht	Hematocrit
IB	Investigator's Brochure
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IM	Intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IT	Intrathecal
LCLA	Low Contrast Letter Acuity
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSC	Mesenchymal Stromal Cells
MSFC	Multiple Sclerosis Functional Composite
MSC-NTF	Mesenchymal Stromal Cells Secreting Neurotrophic Factors
MSWS-12	12 item MS Walking Scale
MVIC	Maximum Voluntary Isometric Contraction
NIV	Non-invasive Ventilation
NTF	Neurotrophic Factors
PT	MedDRA Preferred Term
PTT	Partial thromboplastin time

Abbreviation	Term
Q1	First Quartile
Q3	Third Quartile
RBC	RBC Red blood cells
SAE	SAE Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modality test
SOA	Schedule of Assessments
SOC	MedDRA System Organ Class
T25FW	Timed 25-foot Walk
TBD	To Be Determined
TFL	Tables, Figure and Listings
TEAE	Treatment-Emergent Adverse Event
US	United States
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cells
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

Multiple sclerosis (MS) may be caused by an autoimmune response to self-antigens in a genetically susceptible individual. Symptoms of MS usually appear between the ages of 20 and 40 and affect nearly 1 million individuals in the US. Approximately 50% of MS patients eventually develop progressive disease associated with increasing levels of motor, visual and cognitive functional impairment and disability. Progressive MS can occur at disease onset (primary progressive) or more commonly be preceded by a relapsing disease course (secondary progressive)[1,2]. The loss of mobility and accumulating neurological dysfunction has an enormous impact on social functioning, activities of daily living, employment and socioeconomic status[3].

In progressive MS, the long-term accumulation of brain injury caused by inflammation, demyelination, axonal damage, neuronal degeneration and gliosis in both white and gray matter, is currently without effective therapy. While inflammatory mechanisms predominate in the early stages of the disease, reflected most directly in relapses and magnetic resonance imaging (MRI)-detected lesion activity, in progressive MS there is gradual worsening of disability and neurodegeneration that progresses independent of relapses. Central nervous system (CNS) repair processes do exist in MS; however, they are not able to fully compensate for the damage that is ongoing in most patients.

Currently approved MS treatments primarily target CNS inflammation and are most effective when introduced early in the disease course, before the progressive phase of disease has started and in patients with significant inflammation as measured by standard brain MRI parameters[1]. Treatment strategies to prevent tissue damage or increase repair, remyelination and axonal regeneration, are greatly needed. Cell therapies, due to their combined immunomodulatory, neuroprotective and neuro-regenerative properties, make them an attractive candidate therapy.

BrainStorm has developed a proprietary process based on autologous Mesenchymal Stem Cells (MSC) which are propagated *ex-vivo* and induced to differentiate into neurotrophic factor (NTF) secreting cells, designated MSC-NTF cells (NurOwn®). A repeat dose randomized (1:1) placebo-controlled US phase 3 study of NurOwn® in 200 amyotrophic lateral sclerosis (ALS) patients is currently underway. Study participants are receiving 3 intrathecal (IT) administrations of cells or placebo 2 months apart. Three previous ALS studies have demonstrated the feasibility, safety and tolerability of intrathecal administration of NurOwn and a well characterized safety profile.

BCT-101-US is an open-label single arm multicenter study to evaluate the safety and efficacy of repeated administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors; MSC-NTF Cells) in participants with progressive MS.

This will be the fifth clinical study conducted by Brainstorm Cell Therapeutics (BCT) to study autologous NurOwn® (MSC-NTF cells) in a neurodegenerative disease. The first three completed studies (two open label and one placebo-controlled study) in ALS patients demonstrated the safety of a single dose of NurOwn® administered either intra muscularly or intrathecally or by combined intramuscular (IM) and IT administration.

The ongoing BCT-002-US Phase 3 double blind placebo-controlled study for 200 ALS patients (randomized 1:1) will evaluate the safety and efficacy of three repeat IT transplantations, 2 months apart.

This BCT-101-US study is a Phase 2 open label study that will be conducted at multiple study sites, in 20 participants with progressive MS with expanded disability status scale (EDSS) 3.0-6.5 inclusive at the Screening Visit. After providing informed consent and signing a written informed consent document all participants will be observed for a total of 9-10 months (34-38 weeks). This study design was chosen after comprehensive discussion with MS experts.

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol BCT-101-US.

This SAP was developed in accordance with International Conference on Harmonization (ICH) E9 Statistical Principles for Clinical Trials guideline.

This SAP is being finalized before the first subject is treated and any additional changes will be finalized prior to database lock.

Further information related to the study can be found in the protocol, Case Report Form and other study documents.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of the study is to evaluate safety and tolerability of 3 intrathecal doses of NurOwn® (MSC-NTF cells).

3.1.2. Secondary Objective

The secondary objectives of the study are:

- To evaluate the efficacy of NurOwn® using improvement in either Timed 25-foot walk (T25FW) speed or 9-Hole Peg Test (9-HPT)
- To evaluate the modulation of cerebrospinal fluid (CSF) and blood biomarkers (neurotrophic factors, neurodegenerative, and inflammatory biomarkers) following NurOwn® transplantation
- To evaluate the efficacy of NurOwn® using:
    - The EDSS
    - The 12 item MS Walking Scale (MSWS-12)
    - Physical function (including average daily step count using ActiGraph's CenterPoint Insight Watch [CPIW] wrist wearable sensor)
    - Low Contrast Letter Acuity (LCLA)
    - Symbol Digit Modality Test (SDMT)
    - MSFC Composite Scores

3.2. Study Endpoints

3.2.1. Primary Endpoints

Primary endpoints of this study are assessment of safety and tolerability by analysis of changes in vital signs and physical and neurological examination findings, hematology, blood chemistry, urinalysis, AEs, SAEs, MRI data and changes in concomitant medications (CM).

3.2.2. Secondary Endpoints

Secondary endpoints for the study are efficacy endpoints with the primary efficacy endpoint evaluated as indicated below:

- Percentage of subjects with improvement from baseline to Week 28 in either T25FW or 9-HPT of ≥ 25%.

Section 9.6 provides additional details.

Other secondary efficacy endpoints evaluated include changes from baseline to each post baseline timepoint:

- Percentage of subjects who improve on T25FW by ≥ 25% (Other thresholds such as ≥ 15%, ≥ 20% and ≥ 30% will also be evaluated)

- Percentage of subjects who improve on 9-HPT by ≥ 25% (Other thresholds such as ≥ 15%, ≥ 20% and ≥ 30% will also be evaluated)
- Mean Changes and % Changes in T25FW (ft/sec.)
- Mean Changes and % Changes in 9-HPT (sec.)
- Mean Changes and % Changes in various CSF and blood biomarkers (Biomarkers detailed below)
- Mean Changes and % Changes in EDSS Scores
- Mean Changes and % Changes in EDSS and its Functional System (FS) subscales (Pyramidal, Cerebellar, Brainstem, Sensory, Bowel and Bladder, Visual, Cerebral or Mental, and Ambulation)
- Percentage of Subjects that improve on EDSS by ≥ 1.0 for those with baseline EDSS ≤ 5.5 and improvement ≥ 0.5 for those with baseline EDSS > 5.5 (Note maximum EDSS for subjects enrolled is 6.5 inclusive)
- Mean Changes and % Changes in MSWS-12 Scores
- Percentage of Subjects that improve on MSWS-12 Scores by ≥ 8 points (other thresholds such as improvements of ≥ 7, ≥ 9 points will also be evaluated)
- Mean Changes and % Changes in Daily Step Count as measured by CPIW
- Mean Changes and % Changes in Step Count as measured by CPIW during T25FW
- Mean Changes and % Changes in count per minute of daily activity as measured by CPIW
- Shift Table on time spent in each of the following categories: (Sedentary, Light, Lifestyle, Moderate, Vigorous, Very Vigorous) as measured by CPIW
- Percentage of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute as measured by CPIW
- Mean Changes and % Changes in LCLA Scores
- Percentage of subjects with an increase in LCLA score by ≥ 7 points (other thresholds such as improvements of ≥ 6, ≥ 8 points will also be evaluated)
- Mean Changes and % Changes in SDMT Scores
- Percentage of subjects with an increase in SDMT score by ≥ 4 points (other thresholds such as improvements of ≥ 3, ≥ 5 points will also be evaluated)
- Mean Changes and % Changes in MSFC Composite Z-Scores (25FWT, 9-HPT, SDMT)
- Mean Changes and % Changes in MSFC Composite Z-Scores (25FWT, 9-HPT, SDMT, LCLA)

Section 9.6 provides additional details.

4. STUDY DESIGN

4.1. Summary of Study Design

This is a proof-of concept Phase 2 open-label study that will be conducted at multiple study sites in 20 participants with progressive MS with EDSS 3.0-6.5 (inclusive) at the Screening Visit. After providing informed consent and signing a written informed consent document all participants will be observed for a total of 9-10 months (38 weeks).

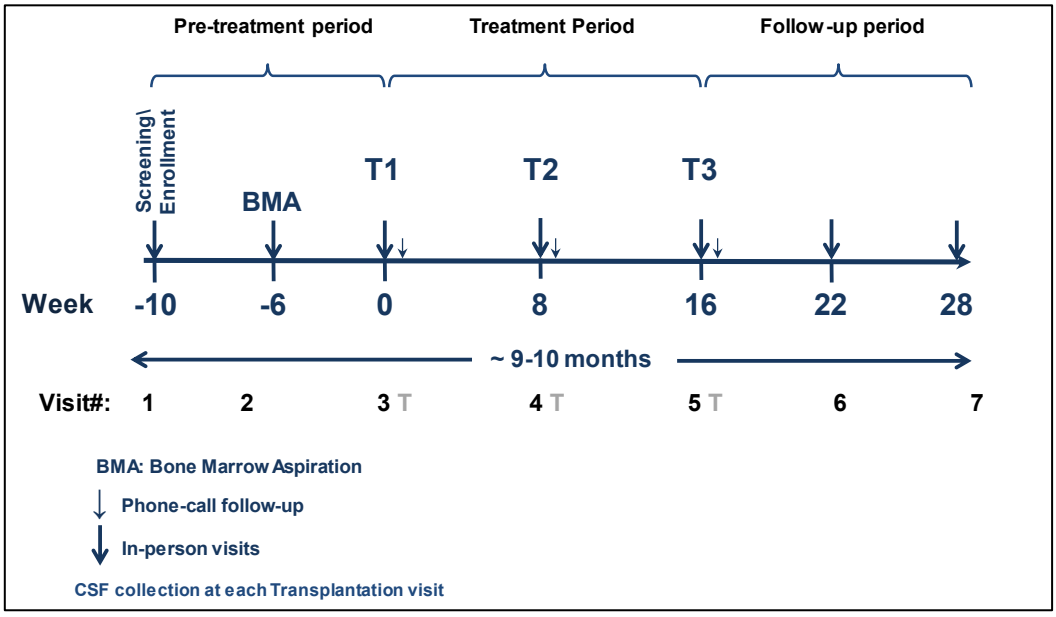
During the up to 10-week pretreatment period patients will be screened and eligibility determined. Approximately 1-4 weeks after the screening visit, bone marrow will be harvested and transferred to the cell manufacturing facility for the isolation and cryopreservation of autologous MSCs.

The first transplantation visit (T1) will occur approximately 6 weeks after the bone marrow aspiration visit (6-10 weeks after screening/enrollment). The subsequent transplantation visits (T2 and T3, at visits 4 and 5) will follow interspaced by approximately 8 weeks (±14 days) each (Figure 1). The subjects will then be followed for 12 additional weeks after the last transplant visit (T3) at two additional visits, approximately 6 weeks apart.

Assessments and procedures that will be performed during the study are provided in Table 2 and Table 3.

Following the third and last treatment, participants will be followed for two additional monthly visits (through week 28) during which the T25FW, 9HPT and other study outcomes (including an MRI assessment at the End of Study visit) will be obtained, along with vital signs, laboratory tests and recording of CMs and AEs [see schedule of assessments (SOA) in Table 2].

Figure 1 Clinical study flowchart



Clinical study flowchart outlining the pre-treatment and the treatment period and the post-transplant follow-up visits. BMA: Bone Marrow Aspiration; T1, T2 and T3, Transplantation 1, 2 and 3. T- Telephone call visit

4.2. Study Drug

The investigational products for this study will be MSC-NTF cells (NurOwn®).

Participants' bone marrow will be aspirated and MSC cells will be isolated from the total bone marrow mononuclear cell population, propagated in culture and induced to secrete NTFs. NurOwn® (MSC-NTF cells) will then be transplanted back into the participant as follows:

- 100-125 x10^6 cells by IT administration

NurOwn® will be provided in a ready-to-use subject-personalized unique treatment package with the appropriate primary and secondary labels. The treatment package consists of one 5 mL syringe for IT transplantation. Each treatment package consists of a ready for-injection syringe containing freshly harvested autologous cultured NurOwn® (MSC-NTF cells) at the dose defined in the clinical study protocol.

4.2.1. Bone Marrow Aspiration

A total of 80 to 100 mL of bone marrow will be aspirated from each participant.

4.2.2. Intrathecal Transplant Procedure

Participants will undergo a standard lumbar puncture followed by IT injection of cells. During the procedure, CSF will be collected prior to administration of cells for biomarker analysis.

4.3. Sample Size Considerations

No formal sample size calculation is performed. Efficacy and safety data on 20 subjects will provide information to inform the design of a future randomized clinical study.

4.4. Randomization

Not applicable. This is an open-label, uncontrolled single arm study.

4.5. Clinical Assessments

The schedule of assessments tables below provides an overview of the protocol visits and procedures.

Table 2: Schedule of Assessments

Study Period	Pre-treatment period		Cells Transplantation period					Post-transplantation follow-up		
Visit	V1	V2	V3	V3T	V4	V4T	V5	V5T	V6	V7[11]
Procedure	Screening/ Enrollment	BMA	Cell Transplantation (T1)	Telephone Call visit	Cell Transplantation (T2)	Telephone Call visit	Cell Transplantation (T3)	Telephone Call visit	Follow-up visit	End of Study Visit
Time Schedule	Week -10-6*	Week -5 to -6	Day 0 - Day 1	Week 1-2	Week 8 (± 14 days)	Week 9-10	Week 16 (± 14 days)	Week 17-18	Week 22 (± 5 days)	Week 28 (± 5 days)
Informed consent	√									
Eligibility criteria	√									
Demographic data	√									
Height	√									
Medical History	√									
MS Medical History [1]	√									
12 lead ECG	√									
Neurological Examination	√									√
Viral safety testing (HIV 1 and 2, HBV and HCV)**	√									
Body weight	√									√
Pregnancy test (for women with childbearing potential)	√									√
Bone marrow aspiration		√								
Transplant (IT)			√		√		√			
CSF collection			√		√		√			
Visual inspection of injection site			√		√		√			
Blood collection for biomarkers			√		√		√		√	
Physical examination	√		√		√		√		√	√
Vital signs[2]	√	√	√		√		√		√	√
Hematology[3]	√	√	√		√		√			√
Blood biochemistry [4]	√		√		√		√			√
Coagulation tests [5]	√	√	√		√		√			√
Prior/Concomitant medication review	√	√	√	√	√	√	√	√	√	√
Adverse events review	√	√	√	√	√	√	√	√	√	√
Urinalysis [6]	√									√
EDSS[7]	√		√		√		√		√	√
C-SSRS	√									√
MRI	√									√
Low Contrast Letter Acuity (LCLA)	√		√		√		√		√	√
MS functional composite[8]	√		√		√		√		√	√
SDMT [9]										
MSWS-12 [10]	√		√		√		√		√	√
Wearable sensor device issued and training	√									
Wearable sensor device	√	√	√	√	√	√	√	√	√	√

Abbreviations: MS=Multiple Sclerosis; EDSS=Expanded Disability Status Scale; CSF=cerebral spinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; HIV=human immune deficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus; IT=intrathecal; V=visit

*Screening Visits scheduling is coordinated with the manufacturing facility

** If applicable must be repeated within up to 7 days prior to BMA

1 MS Medical History to collect type and duration of MS symptoms and Date of Diagnosis

2 Pulse rate, Blood pressure (Respiratory rate, Body temperature)

3 Hematology: Complete blood count (red blood cells with indices, white blood cells with differential and platelet count, hemoglobin, hematocrit)

4 Blood Biochemistry: At V1 and V7: Sodium, potassium, chloride, glucose, BUN, creatinine, bicarbonate, calcium, total bilirubin, AST, ALT, alkaline phosphatase, uric acid, total cholesterol, HDL, LDL. At V3, V4 and V5: sodium, potassium, chloride, glucose, BUN, creatinine

5 Coagulation: PT, PTT, INR.

6 Urinalysis - Specific Gravity, pH, glucose, protein, ketones, blood.

7 EDSS-Expanded Disability Status Scale.

8 MSFC including T25FW and 9-HPT

9 Symbol Digit Modality Test (SDMT).

10 12 item MS Walking Scale (MSWS-12).

11 An Early Termination (ET) visit will be conducted only for participants who discontinue the study after the first treatment, post Visit 3. The ET visit will include all the procedures required at study Visit 7.

Table 3: Detailed Schedule of Assessments for Cell Transplantation Visits (V3, V4, and V5)

Estimated Time	xx:00-yy:00	12:00	14:00	20:00	08:00	12:00
Time\ Procedure	**Up to 8 hours before transplant**	**Hr. 0**	**Hr. 2 (± 15 minutes)**	**Hr. 8 (±15 minutes)**	**Hr. 20 (±30 minutes)**	**Discharge/up to Hr. 24**
Admit to In-patient Facility	√					
Physical Examination	√					√
Concomitant medication review	√					√
Hematology[3]	√					
Blood biochemistry[4]	√					
Coagulation[5]	√					
Blood collection for biomarkers	√				√	
Vital signs[2]	√		√	√	√	√
Adverse events review[6]	√		√	√	√	√
Cell Transplant IT		√				
Retention of CSF sample		√				
Visual inspection of injection site			√		√	
Discharge from Inpatient Setting						√

Abbreviations: BUN = blood urea nitrogen, CSF = cerebrospinal fluid, INR = international normalized ration, IT = intrathecal, PT = prothrombin time, PTT = partial thromboplastin time

*Hematology, biochemistry and coagulation labs are to be drawn and checked before transplant

**To be determined for each study site

1. Hematology: Complete blood count (red blood cells with indices, white blood cells with differential and Platelet count, hemoglobin, hematocrit)
3. Sodium, potassium, chloride, glucose, BUN, creatinine
4. Coagulation - PT, PTT, INR
5. Pulse rate, Blood pressure (Respiratory rate, Body temperature)

5. PLANNED ANALYSES

5.1. Interim Analyses

There are no formal interim analyses planned for this study, however since the study is an open label single arm study, analyses to evaluate safety and efficacy will continue during the study. There are no formal stopping rules included in the study.

5.2. Analyses for Data and Safety Monitoring Board (DSMB) Meetings

An independent DSMB will monitoring the safety of the trial. Select Tables, Figures and Listings will be generated and provided to the DSMB. Additional details of the list of tables, figures and listings (TFLs) will be agreed to with the DSMB and included in the DSMB Charter. A separate document will provide the mock shells of these TFLs to the DSMB. The schedule of the DSMB meetings will be detailed in the DSMB charter. Currently the first data meeting of the DSMB is planned when 50% (10) subjects complete one month after the first treatment. Any serious AEs are reported to the DSMB on a monthly basis, except deaths which will be reported as the sponsor is made aware of them.

The DSMB charter will also detail what will be provided to the DSMB on a monthly basis.

5.3. Final Analyses

Final analysis will be performed after database lock.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

This section addresses the definitions, algorithms, imputations, and conventions that will apply to the analysis and handling of the data in general. Rules that are data specific will be addressed in the detailed discussions of individual summary tables.

This SAP and all TFLs created will use U.S. spellings.

6.1. General Summary Table and Individual Subject Data Listing Considerations

Summary tables and listings (e.g., post text tables and individual subject data listings are prepared according to ICH Guideline E3) include a "footer" providing explanatory notes that indicate as a minimum:

1. Date of data extraction.
2. Date and time of output generation.
3. SAS program name, including the folder that generates the output. The full path may be replaced by a partial path before final run if requested by sponsor.
4. Any other output specific details that require further elaboration.

Summary tables will also include reference(s) to the subject data listing(s) that support the summary data.

Post text tables also include reference(s) to the subject data listing(s) that supports the summary data. The data extraction date links the output to the archived database that is frozen to ensure the replication of the results.

All Tables will display Treatment in one group labeled as "NurOwn®".

Row entries in post text tables are always displayed for every category even if no data exists for any subjects (e.g., a row with all zeros will appear).

The summary tables will clearly indicate the number of subjects to which the data apply along with an indication for the number of subjects with missing data.

Summary tables for medications are coded according to the standard World Health Organization Drug Standard Dictionary [WHODD] Version September 2018. AE verbatim (reported) terms are coded to preferred terms (PT) and body/organ systems using Medical Dictionary for Regulatory Activities Terminology (MedDRA) Version 21.1.

Individual subject data listings will include all demographic, background, safety and efficacy data collected in the study, except for data collected on ActiGraph's CPIW which will only include summary data for each day and during the T25W. Individual Subject Data Listings, as a minimum, are sorted by Subject ID and Visit (Week), where applicable.

When missing or partial dates are imputed, the listings will display both the missing or partial dates as well as the imputed dates.

Any data derived for analyses will also be included with the raw data in the listings and flagged as derived data.

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

The default convention is to number tables and listings and will use a decimal system to reflect main levels of unique tables and listings and sub-levels of replicate tables and listings with two digits per level and not more than 2 decimal digits (e.g., Table XX.YY.ZZ).

1. The first level number will be consistent with the corresponding CSR appendix in which the tables or listings will appear. For example, the post text tables usually occupy Appendix 14 and the individual subject data listings are put in Appendix 16.2. All post text tables will have a main number level 14 and listings 16.2. The subject disposition table is usually first in the first section of the report and will be numbered Table 14.1.1 The supportive subject data listing would be Listing 16.1. A subset of disposition table by site would have the number Table 14.1.2, etc. No more than 4 decimal digits will be used in numbering Tables and Listings (e.g. 14.a.b.c.d).
2. Subject disposition, baseline and demographics Tables will appear as the second level number (Table 14.1 series). Efficacy will come next (14.2 series) followed by safety (table 14.3 series). Similar conventions will be applied to the subject data listings.
3. The title will be complete, accurate, and concise. The last line of the title will provide the analysis group being summarized (e.g., All Subjects, Safety Population, Modified Intent-to-Treat Population or Efficacy-Evaluable Population). If possible, the units of measurement for data contained in the table can appear in parentheses to conserve space in the body of the table. For example, the summary of vital signs title could read "Summary of Sitting and Standing Blood Pressure (mmHg) and Heart Rate (bpm)." Whether in the title or body of a table or listing, units must always be specified for all appropriate data.
4. When relevant, variables being summarized, and statistics reported will appear in the left most column of a table. The next columns will report the data from left to right for the investigational drug by doses and for all treated subjects, respectively.

The definition of all derived variables and decodes for coded data must appear either on the Table or Listing. Due to space limitations, tables and listings may require a page of notes as a one-time preface to the output.

Tables and Listings will be self-contained and all-important information to review the Table or Listing will either be in the titles or footnotes.

6.3. Data Management

Data from the study will be entered into Bioclinica electronic data capture (EDC) version 5.6, a validated electronic 21CFR Part 11 compliant database. Data review, coding, and logic, range, cross-form, and consistency checks will be performed to ensure quality of the data. Adverse events (AE) and medications will be coded using MedDRA version 21.1 and the WHODD September 2018, respectively.

Derived datasets will be created using (SAS®) software. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

6.4. Data Presentation Conventions

Continuous variables (e.g. age) are summarized using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum and maximum).

Categorical variables (e.g. race) are summarized using counts and percentages. Percentages are calculated using the total subjects within the dose group (or dose group and relevant subgroup when appropriate) being presented.

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean, first quartile (Q1), median and third quartile (Q3) values are formatted to one more decimal place than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value. For measure of variation, e.g. SD, use two more decimal places than the measured value, unless numbers are in at least 100s and there are space constraints in which case 1 decimal place is fine.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- Wherever possible, data will be decimal aligned or left aligned or as appropriate to best display the data and column headers. Parenthesis will also be aligned appropriately for best display.
- Hypothesis testing to determine if changes from baseline were statistically significant and comparing these against matched historical controls will be performed and presented in select Tables either as post-text Tables or in the CSR depending upon availability of historical data. Similar additional analyses on the percentage of responders from the current study against matched historical controls may be included in the CSR. Subjects from a historical database will be selected by matching key screening or baseline characteristics.
- P-values, if applicable, will be presented to 3 decimal places. If the p-value is less than 0.001 then it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

The table and listing shells and table of contents provide the expected layout and titles of the tables, listings and figures.

Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation.

The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

6.5. Analysis Populations

6.5.1. Safety Population

All safety analyses will be conducted on the Safety Population, which is defined as all participants who were enrolled, and had at least one transplantation performed.

6.5.2. Modified Intent to Treat (mITT) Population

All efficacy analysis will be conducted on the mITT population, which is defined in this study as all participants who are in the safety population and have at least one T25FW or 9-HPT assessment post baseline.

6.5.3. Efficacy Evaluable (EE) population

All efficacy analysis will be conducted on the EE population, which is defined as a subset of the mITT population that receive all 3 treatments and do not have any important protocol deviations impacting efficacy evaluation. If EE population is same as mITT population, then only mITT population would be used for all efficacy analysis.

6.6. Baseline Definition

The baseline visit will be defined as the most recent assessment prior to receiving the first transplantation at Visit 3.

6.7. Derived and Transformed Data

6.7.1. Baseline Age

Due to data protection requirements only year of birth and age at time of signing consent will be captured on the eCRF and no computation of age will be necessary.

6.7.2. Study Day

If the date of interest (date of visit, date of start of transplant, date of AE, etc.) occurs on or after the first transplantation date then study day will be calculated as (date of interest – date of first transplantation) + 1. If the date of interest occurs prior to the first transplantation date, then study day will be calculated as (date of interest – date of first transplantation). Study Day 1 is the date of first transplantation. There is no study day 0.

6.7.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result)*100 as long as baseline is non-zero. If baseline is 0, change from baseline is defined as missing.

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.7.4. Multiple Assessments

For detection of clinical abnormalities all available data including from unscheduled visits will be used and if summarized by timepoint, the most abnormal value will be considered. When summarizing low and high abnormality, both most abnormal low and high values will be displayed separately in 6 categories (missing, clinically significant low, not clinically significant low, normal, not clinically significant high, clinically significant high). If a subject had both low and high abnormalities, then only the worst value would be displayed in the appropriate category of the abnormality and shift tables, but all abnormalities will be identified in the listings.

6.8. Handling of Missing Data

Missing values with the exception of dates will not be imputed.

6.8.1. Missing Start and Stop Dates for Adverse Events and Concomitant Medications

The following imputation rule will be used in this study:

For onset or start dates as well as end or stop dates for AEs or Medications, a conservative approach will be used, where if an event can be considered as being on treatment it will be assumed to be so.

For onset or start dates for AEs or Medications, the following rules will be used to impute partial dates:

a) If month and year are known, but the day is unknown, the day will be assumed to be the 1st. unless the treatment was started that month of the same year in which case the day will be set to the day of start of treatment.

b) If only the year is known but both day and month are missing, the day and month will be assumed to be 1st January, unless the treatment started that year, in which case the day and month will be imputed to be the treatment start day and month.

For end or stop dates the following will be used to impute partial dates:

a) If month and year are known, but the day is unknown, the day will be assumed to be the last day of the month, unless the date of last treatment is in the same month and year, in which case the day of last treatment will be used to impute the end or stop day.

b) If only the year is known but both day and month are missing, the day and month will be assumed to be 31st December, unless the date of last treatment is in the same year, in which case the day and month of last treatment will be used to impute the end or stop day and month.

In addition:

If an AE start date is completely missing or it is unclear whether the event occurred prior to or in the treatment period, the AE will be assumed to be treatment emergent (after initiation of first treatment).

If a medication end date is completely missing or it is unclear whether the medication was taken prior to or in the treatment period, the medication will be assumed to be taken during the treatment period as a “concomitant medication”.

7. STUDY POPULATION

7.1. Subjects Disposition

Subject disposition will be summarized descriptively as follows:

- A summary of the number of subjects in each of the analysis populations.
- The number and percentages of subjects who signed informed consent but were not treated.
- The number and percentages of subjects who had Bone Marrow Aspiration but were not treated.
- The number and percentage of subjects who (a) completed study (b) discontinued from the study by number of treatments prior to discontinuation. For those who discontinued from the study, the primary reason for discontinuation from the study will be presented.
- If any subjects are re-screened this will be footnoted in the Table along with the Subject-ID.

7.2. Screen Failures

Screen failures are potential study subjects who provide written informed consent authorization and complete some or all screening procedures but are determined to be ineligible for treatment with study drug or decide not to continue prior to first treatment.

7.3. Protocol Deviations

Summary of all important protocol deviations by type of deviations will be summarized in a Table and details provided in a listing.

7.4. Demographic and Baseline Characteristics

The demographic and baseline characteristics data collected at the Screening Visit (V1) will be presented for the Safety population. The continuous variables, ex., age in years, will be summarized using descriptive statistics (n, mean, SD, first quartile, median, third quartile, minimum, and maximum). The discrete variables, ex., gender will be summarized using counts and percentages.

Baseline electrocardiogram (ECG) results will be presented for each subject in a listing.

Baseline vital signs, physical examination and laboratory results will be in the Safety Tables and not separately in the Demographics and Baseline Characteristics sections.

7.5. Listing of Subject Inclusion and Exclusion Criteria

For subjects who did not meet inclusion or exclusion criteria and were not treated, a listing will indicate which criteria they did not meet.

7.6. Medical History and Medical Conditions Present at Entry

Medical history will be coded using the MedDRA, version 21.1. Counts and percentages of subjects with each medical history will be summarized using MedDRA system organ class (SOC) and PT for the Safety population. SOCs will be ordered alphabetically and PTs within SOCs will be ordered by descending incidence of all subjects.

MS Medical History would be presented separately in a listing for each subject. It will include the date of onset of MS symptoms, date of diagnosis of MS, whether MS is Primary Progressive MS (PPMS) or Secondary Progressive MS (SPMS), and if SPMS, date of conversion to SPMS.

7.7. Prior and Concomitant Medications

All medications (e.g., both prior and concomitant) will be coded with respect to the Anatomical Therapeutic Chemical (ATC) drug classification coding system and the data summarized by level 2 and PT. Therefore, all possible ATC codes for a given medication by the WHODD Version September, 2018 will be displayed.

The displays of medications will be performed without any regard to the indication the medication was taken for.

Separate Tables will display prior medications and CMs using the Safety Population.

7.7.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Missing or partial Concomitant and Other Medication Start and Stop Dates will be imputed as described in Section 6.8.1.

7.8. Exposure and Compliance to Study Drug

A summary of the number of IT administrations received will be presented using counts and percentages for the Safety Population.

The duration in months (exposure) between the first and third IT administration will be presented using descriptive statistics for the Safety population.

Compliance rate (%) will be calculated for each subject as follows:

(Total number of IT administrations) / (Expected number of administrations) *100.

8. SAFETY AND TOLERABILITY

All safety analyses will be based upon the Safety Population.

All AEs will be coded to SOC and PT using the MedDRA, version 21.1.

A Treatment-emergent adverse event (TEAE), referred to subsequently as just TEAE or AE is an AE that occurs for the first time after initiation of first treatment or if it had occurred prior to initiation first treatment, it worsens in severity after initiation of first treatment.

AE's that occur prior to initiation of first treatment will only be in the listings and not included in any summary Tables.

AE's related to the Bone Marrow Aspiration will be included in a separate listing.

When evaluating changes in continuous safety parameters (such as laboratory measurements, vital signs, ECGs, etc.) , Baseline will be defined as the last measurement prior to first transplantation (i.e., prior to initiation of treatment).

Additional details for analysis of safety data are detailed below.

8.1. Overall Summary of Tolerability

The overall summary of tolerability table will present data by the NurOwn® group. Entries in this table will include:

1. Number of TEAEs
2. Subjects with at least one
    a. Adverse event including procedure related AEs
    b. Procedure related AEs
    c. AE excluding procedure related AEs
    d. AE related to the study medication
    e. Severe AEs including procedure related Severe AEs
    f. Severe AEs related to procedure
    g. Severe AEs excluding procedure related Severe AEs
    h. Severe treatment related AEs
    i. Serious AEs
    j. Serious treatment related AEs
    k. AEs leading to study discontinuation
    l. MS relapses
    m. AEs leading to death

The above summaries will include the number of events as well as number and percentage of subjects experiencing at least one TEAE.

The subject data listing provides a complete list of all AEs as recorded in the CRF and supports this table and all other AE summary table subsets.

8.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Each Table will display the number and percentage of subjects who experience AEs with rows displaying the MedDRA primary SOC and PT. A subject who experiences multiple TEAEs coded to the same PT within the same SOC will be counted only once for that PT (or SOC for SOC rows). The number and percentage of subjects experiencing any TEAE will also be provided with each subject being counted only once. All percentages will use the number of subjects in the safety population as the denominator. Unless otherwise specified, in the summary Tables, SOCs will be sorted by alphabetical order and within SOC by PT alphabetically.

8.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

The analysis of TEAEs will be repeated for the following AE categories:

- All AEs sorted by SOC and PT including procedure related AEs
- Procedure related AEs sorted by SOC and PT
- All AEs sorted by SOC and PT excluding procedure related AEs
- All AE's sorted by descending incidence rate in PT
- Serious AEs sorted by SOC and PT
- AE's by severity (mild, moderate, severe) sorted by SOC and PT (A subject with multiple events within a SOC or PT will be reported under the maximum severity) including Procedure Related AEs
- Procedure Related AE's by severity (mild, moderate, severe) sorted by SOC and PT (A subject with multiple events within a SOC or PT will be reported under the maximum severity)
- AE's by severity (mild, moderate, severe) sorted by SOC and PT (A subject with multiple events within a SOC or PT will be reported under the maximum severity) excluding Procedure Related AEs
- AEs by relationship to study medication sorted by SOC and PT (A subject with multiple events within a SOC or PT will be reported under the greatest relationship to study medication)
- AEs leading to study discontinuation sorted by SOC and PT

All listings will be based on the Safety Population and will include all data captured on the eCRF as well as MedDRA information (i.e. SOC and PT). Treatment-emergent AEs will be flagged in this listing. Separate listings will be created for each of the following:

- All AEs
- SAEs
- AEs related to the study medication
- Procedure related AEs
- Serious related AEs
- Severe AEs

- Severe related AEs
- AEs leading to death (i.e. AEs with seriousness, "Death" or outcome "fatal" according on the AE page)
- AEs leading to study discontinuation

A listing with no subjects will display "No Subjects in Listing".

8.3. Routine Laboratory Data

The analyses of the safety laboratory will be performed using the Safety Population. Multiple assessments within a visit or time interval will be handled as described in Section 6.7.4.

Mean Changes and % Changes from baseline to each post baseline timepoint in each laboratory assessment that is a continuous variable will be summarized along with other descriptive statistics for continuous variables.

Additionally, chemistry and hematology parameters will be categorized as low, normal or high according to laboratory range specifications. In addition, Investigator assessment of whether the abnormality was clinically significant will be recorded.

The number and percentage of subjects will be presented at each assessment time point for the safety population using the following categories:

- missing data
- clinically significant low abnormality
- non-clinically significant low abnormality
- normal values
- non-clinically significant high abnormalities
- high clinically significant abnormalities

In addition shift Tables will summarize clinically significant abnormalities between baseline and post baseline value using the above categories and the worst values post baseline. Note, this tabulation is not by visit.

Urinalysis tests that are recorded as continuous parameters like pH and specific gravity will be analyzed as above. All other urinalysis parameters will just be included in the listings.

Coagulation parameters will be analyzed as above.

Laboratory values outside the normal range will be displayed in a separate listing with clinically significant values flagged. Determination of clinical significance will be made by the Investigator and recorded in the eCRF.

Laboratory parameter units will be standardized to conform to the Table below:

Laboratory parameters for safety investigations will be analyzed in the standardized units given below:

Blood Biochemistry:

- Alkaline phosphatase U/L
- Alanine aminotransferase (ALT) U/L
- Aspartate aminotransferase (AST) U/L

- Bicarbonate mmol/L
- Blood urea nitrogen (BUN) mg/dL
- Calcium mmol/L
- Chloride mmol/L
- Creatinine µmol/L
- Glucose mmol/L
- High-Density Lipoprotein (HDL) Cholesterol mmol/L
- Low-Density Lipoprotein (LDL) Cholesterol mmol/L
- Potassium mmol/L
- Sodium mmol/L
- Total Bilirubin µmol/L
- Total Cholesterol mmol/L
- Uric Acid mg/dL

Hematology:

- Basophil Differential %
- Basophils (Absolute) 10^9/L
- Eosinophil Differential %
- Eosinophils (Absolute) 10^9/L
- Erythrocytes (RBC) 10^{12}/L
- Hematocrit Fraction
- Hemoglobin g/L
- Leucocytes (WBC) 10^9/L
- Lymphocyte Differential %
- Lymphocytes (Absolute) 10^9/L
- Monocyte Differential %
- Monocytes (Absolute) 10^9/L
- Neutrophil Differential %
- Neutrophils (Absolute) 10^9/L
- Platelets 10^9/L

Coagulation:

- Prothrombin Time (PT) sec
- Partial Prothrombin Time (PPT) sec
- International Normalized Ratio (INR)

8.4. Vital Signs

Mean Changes and % Changes from baseline to each post baseline timepoint in each Vital Signs assessment will be summarized along with other descriptive statistics for continuous variables.

Additionally, vital signs parameters will be categorized as low, normal or high according to the following ranges for clinically notable vital sign abnormalities

VITAL SIGNS		NOTABLE ABNORMALITIES Change Relative to baseline or Absolute Levels
Pulse (beats/min)		Either ≥ 120 + increase ≥ 15 or > 130 Either ≤ 50 + decrease ≥ 15 or < 40
Blood pressure (mmHg)	Systolic	Either ≥ 180 + increase ≥ 20 or > 200 Either ≤ 90 + decrease ≥ 20 or < 75
	Diastolic	Either ≥ 105 + increase ≥ 15 or > 115 Either ≤ 50 + decrease ≥ 15 or < 40
Weight		Either ≤ or ≥ 10%

8.5. Physical Examination

Physical exam abnormalities will be displayed in a listing.

8.6. 12-Lead Electrocardiogram

No analyses of 12-Lead ECG parameters will be performed since it is conducted only at screening visit. A listing by subject will be presented.

8.7. MRI analysis

MRI Data will be analyzed for safety by looking at the following change from baseline to end of study:

- Mean Changes in number of new or enlarging FLAIR lesions on MRI
- Percentage of subjects with ≥ 1, ≥ 2, ≥ 3 new or enlarging FLAIR lesions on MRI
- Mean Changes in active FLAIR lesions (new + enlarging) on MRI
- Percentage of subjects with ≥ 1, ≥ 2, ≥ 3 active FLAIR lesions (new + enlarging) on MRI
- Mean Change in Total volume of new FLAIR lesions on MRI
- Mean Change in Total volume of FLAIR lesions on MRI

8.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a rating-based interview assessment tool that evaluates suicidal ideation and behavior.

The C-SSRS questionnaire includes five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent as a standard. Additionally, it includes a suicidal behavior lethality rating and a suicidal ideation intensity rating. It is a safety questionnaire that addresses concerns for various regulatory bodies.

Since this is a small study, with no control arm, C-SSRS data will just be displayed in a listing.

8.9. Other Safety Assessments

Pregnancy Test

Pregnancy test results will be listed by subject.

Neurological Examination

Neurological examination results will be listed by subject.

Viral Safety Test

Viral safety test results for Human immunodeficiency virus (HIV) 1 and 2, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) will be listed by subject.

9. EFFICACY

9.1. General Considerations

Descriptive statistics for continuous and categorical variables will be presented as described in Section 6.4.

Inferential statistical tests will be performed at Type I error $\alpha = 0.05$ (Two-sided). Since this is a single arm, open label study, hypothesis testing will be performed against a historical database by selection of subjects matched on key screening or baseline characteristics.

9.2. Analysis of Primary Efficacy Endpoint

The primary objective and endpoints in the study are assessments of safety. The secondary objective and endpoints are assessments of efficacy.

The first secondary endpoint is considered the primary efficacy endpoint for this study.

Efficacy analyses will be performed using the modified mITT and EE populations. If mITT and EE populations are the same then, all efficacy analysis will be performed using mITT population only.

The primary efficacy endpoint will be a responder analysis to see if subjects improve in walking speed as measured by time to complete T25FW (ft/sec.) or improve in finger (fine manual) dexterity as measured by time to complete the 9-HPT (sec.)

A subject will be defined as a responder to study drug if their T25FW walking speed or 9-HPT improves by 25% or more between baseline and Week 28. An improvement of 25% is considered clinically meaningful for MS patients[4,6].

All deaths related to disease progression or treatment will be defined as non-responders.

The T25FW, 9-HPT, LCLA and SDMT are part of the current Multiple Sclerosis Functional Composite (MSFC) and described in Additional detail in the BCT-101-US Protocol, Sections 15.2.1, 15.2.2, 15.2.3, 15.2.6, and 15.2.7 in Appendix 1.

The T25FW is a quantitative mobility and leg function performance test based on a timed 25 foot-walk. It is the first component of the MSFC to be administered at each visit. The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the subject has reached the 25-foot mark. The task is immediately administered again by having the subject walk back the same distance. T25FW score is the average in seconds of the two successive trials. Subjects may use assistive devices when doing this task. An increase in speed for T25FW is considered an improvement.

The MSFC uses a z-score transformation which will used in assessing the changes in the MSFC.

The 9-HPT is a brief, standardized, quantitative test of upper extremity function. It is the second component of the MSFC to be administered at each visit. Both the dominant and non-dominant hands are tested twice. The participant is seated at a table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the participant picks up the nine pegs one at a time as quickly as possible,

puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. A decrease in time to complete the 9-HPT is considered an improvement.

9.3. Testing Statistical Assumptions Including Comparability at Baseline

Not applicable since BCT-101-US is an open label single arm study with 20 participants.

9.4. Subgroup Analyses

No subgroup analysis is planned because of the small sample size (20 subjects).

9.5. Multiple Comparisons and Multiplicity

Not applicable since BCT-101-US is an open label single arm study with 20 participants.

9.5.1. Sensitivity Analyses of the Primary Efficacy Results

Select sensitivity analyses may be performed on the primary efficacy results if there is missing data or protocol deviations that can impact results.

9.6. Analysis of the Secondary Efficacy Endpoints

T25FW and 9-HPT

Secondary efficacy endpoints are listed in Section 3.2.2. This section provides additional details.

In addition to the primary efficacy endpoint evaluated at Week 28, the percentage of subjects with improvements from baseline to each post baseline timepoint in either T25FW or 9-HPT of ≥ 15%, ≥ 20% and ≥ 30% will also be evaluated.

Other thresholds may be considered to define responder analyses for the efficacy endpoints if the above are deemed to be too low or too high.

As indicated in Section 3.2.2, in addition to determining if a subject was a responder on either T25W or 9-HPT at each timepoint, these two efficacy assessments will be separately evaluated at each timepoint to see improvements in each of them.

- Percentage of subjects who improve on T25FW by ≥ 25% (Other thresholds such as ≥ 15%, ≥ 20% and ≥ 30% will also be evaluated)
- Percentage of subjects who improve on 9-HPT by ≥ 25% (Other thresholds such as ≥ 15%, ≥ 20% and ≥ 30% will also be evaluated)

In order to determine the amount of change or % change from baseline to each post baseline timepoint, mean changes in T25FW from baseline to each post baseline timepoint will be summarized in addition to other descriptive statistics for continuous variables. This will be repeated for the 9-HPT. In addition, mean changes in feet per second will be summarized as noted above for the timed walk.

Biomarkers

CSF and/or serum samples will be collected for determining the concentration of neurotropic factors, inflammatory markers, miRNA, etc. collectively referred to as biomarkers.

Details of biomarker analyses will be specified subsequently.

Biomarkers to be assessed include the following:

Biomarker Type	CSF	Serum
MSC-NTF derived Neurotropic Factors	BDNF, GDNF, HGF, LIF, VEGF, TSG-6, G-CSF	BDNF, GDNF, HGF, LIF, VEGF, TSG-6, G-CSF
Inflammatory Biomarkers	MCP-1, SDF-1, CHIT-1, TNF- α, sCD27 and a full panel of cytokines, chemokines and regulatory proteins	Full panel of cytokines, chemokines and regulatory proteins
miRNA	miRNA panel	miRNA panel
Neurodegeneration	NfL, NfH, GFAP	NfL, NfH, GFAP

Expanded Disability Status Scale (EDSS)

Mean Changes and % Changes from baseline to each post baseline time point in EDSS Scores will be summarized along with other descriptive statistics for continuous variables.

In addition Subjects that improve on EDSS by $\geq$ 1.0 for those with baseline EDSS $\leq$ 5.5 and improvement $\geq$ 0.5 for those with baseline EDSS > 5.5 (Note maximum EDSS for subjects enrolled is 6.5) between baseline and each post baseline time point will be summarized. The EDSS is a 10 point scale with half point increments. Other thresholds for improvements may also be explored.

A shift Table will summarize changes in each of the FS subscales (Pyramidal, Cerebellar, Brainstem, Sensory, Bowel and Bladder, Visual, Cerebral or Mental, and Ambulation) from baseline to each post-baseline timepoint. EDSS is widely used as an outcome measure in MS. A 1.0-point change in the EDSS (for those with baseline EDSS $\leq$ 5.5) or 0.5-point change in EDSS (for those with baseline EDSS >5.5) are considered clinically meaningful[5].

The EDSS is an objective approach to quantify the level of physical disability in MS. It provides a total score on a scale that ranges from 0 (no disability) through 1 to 10 (death due to MS) in 0.5-point steps. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability.

In addition, it also provides eight subscale measurements called FS scores. The levels of function within each category refer to the eight FSs affected by MS: Pyramidal (motor function) (P); Cerebellar (C11); Brainstem (BS); Sensory (S); Bowel and Bladder (BB); Visual (V); Cerebral or Mental (Cb); Ambulation.

For additional detail see Protocol, Sections 15.2.4 in Appendix 1.

Multiple Sclerosis Walking Scale (MSWS-12)

Mean Changes and % Changes from baseline to each post baseline timepoint in MSWS-12 Scores will be summarized along with other descriptive statistics for continuous variables.

Percentage of Subjects that improve on MSWS-12 Scores by ≥ 8 points between baseline and each post baseline time point. A 7 point change in MSWS-12 is considered clinically meaningful[9]. Other thresholds such as improvements of ≥ 7, ≥ 9 points will also be presented.

The MSWS-12 is a patient-reported outcome measure of the walking limitations due to MS during the past 2 weeks. It contains 12 questions that assess the impact of MS on different aspects of walking function and quality.

Total administration time should be approximately 5 minutes. Activities are rated by participant from 1 (not at all) to 5 (extremely) and summed to calculate a total score using a scale from 0 to 60 (ranging from low to high impact on walking). This score is then divided by 60 and multiplied by 100 to get a score between 0 and 100.

If a subject completes at least 6 items out of 12, the score is considered valid, otherwise if less than 6 items are completed the total score is considered missing.

If a subject does not complete all 12 items but does complete at least 6 items their total score is divided by the maximum score for the items completed and multiplied by 100.

Physical Activity as Measured by ActiGraph's CenterPoint Insight Watch (CPIW)

ActiGraph's CPIW (Wrist Sensor) is a medical-grade wearable physical activity, mobility, and sleep behavior monitoring FDA 510(k) cleared Class II medical device used for clinical research.

It will be issued to eligible subjects at Visit 1 with instructions on its use. The device is to be worn on the wrist of the non-dominant hand, throughout the duration of the study. The device will be returned to the site at Visit 7, the final study visit.

Subjects have the option to either take it off while they sleep or keep it on. It is water resistant so may be worn during showering.

The device contains an accelerometer and measures movements on the X, Y and Z coordinates.

These are then converted to various measures of physical activity, mobility and sleep quality. The device will allow to measure changes in mobility and physical activity following each treatment.

Analysis will include changes and % changes from baseline to each post baseline timepoint as well as between prior to each treatment and each week following it. Due to outliers, analyses may be performed including and excluding outliers.

Baseline will be the average of valid data from up to 7 days prior to the first treatment (V3), excluding the day of treatment.

Pre-treatment assessments will be the average of valid data from up to 7 days prior to the second (V4) and third treatments (V5), excluding the days of treatment.

Post treatment assessments will be based upon the average of valid data from each 7-day interval following each treatment visit (not including the day of visit).

A daily assessment will be considered valid if the device was worn for at least 4 hours.
Data from valid days of assessments will be scaled by taking the level of activity, dividing it by the number of hours the device was worn while awake and multiplying it by 16 (average waking period).

- Analyses will summarize mean changes and % changes and other descriptive statistics for continuous variables from baseline to each post baseline week in Daily step count averaged over valid data during 7 days as indicated above
- Count per minute of daily activity averaged over valid data during 7 days as indicated above

Mean changes and % changes and other descriptive statistics for continuous variables in Daily Step Count from baseline to each successive T25FW
Improvements will also be evaluated by the following categorical analyses:

- Shift Table on time spent in each of the following categories: (Sedentary, Light, Lifestyle, Moderate, Vigorous, Very Vigorous)
- Percentage of time spent in light to vigorous physical activity based on a threshold of > 100 activity counts per minute

Additional analyses using data collected and derived from the Center Point Insight Watch including improvements is sleep quality may be performed.

Low Contrast Letter Acuity (LCLA)

Mean Changes and % Changes from baseline to each post baseline timepoint in LCLA Scores will be summarized along with other descriptive statistics for continuous variables. The LCLA score is an integer between 0 and 70 and indicates the correct number of letters identified.

The scores are recorded for the right eye, left eye and both eyes combined. These will be analyzed for the three settings 100%, 2.5% and 1.5%.

Additional categorical analyses will summarize the number and percentage of subjects with an improvement (increase) in LCLA score by ≥ 7 letters. A 7 letter change in LCLA is considered clinically meaningful[8]. Other thresholds such as improvements of ≥ 6, ≥ 8 letters will also be presented.

Sloan LCLA charts are administered binocularly or each eye can be tested individually. The charts are placed on a retro-illuminated cabinet, eliminating the need for standardized room lighting, or on the wall in front of the participant. Participants are seated 2 m away and asked to read the letters aloud proceeding top to bottom and from left to right until they can no longer see the letters.

Total administration time, for a typical MS patient, is approximately 10–15 minutes to complete, when testing each eye individually and binocular vision for two different contrast levels. The

score for each chart is quantified as the number of letters identified correctly with a maximum score of 70 letters.

Symbol Digit Modalities Test (SDMT)

Mean Changes and % Changes from baseline to each post baseline timepoint in SDMT Scores will be summarized along with other descriptive statistics for continuous variables.

Additional categorical analyses will summarize the number and percentage of subjects with an increase in SDMT scores by ≥ 4 points. A 4 point change in SDMT is considered clinically meaningful[7]. Other thresholds such as improvements of ≥ 3, ≥ 5 points will also be presented.

The SDMT involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures.

Total administration time should be approximately 5 minutes.

MSFC Composite Score

Two composite scores will be computed for the MSFC. One composite will include the T25FW, 9-HPT and SDMT and a second composite will include the T25FW, 9-HPT, SDMT and LCLA.

The MSFC Composite Score in the first case is computed as follows:

MSFC Score = {(Average (1/9-HPT) - Baseline Mean (1/9-HPT) / Baseline Std Dev (1/9-HPT) + { - (Average 25-Foot Walk - Baseline Mean 25-Foot Walk) / Baseline Std-Dev 25-Foot Walk} + (SDMT - Baseline Mean SDMT) / Baseline Std Dev SDMT} / 3.0

Note: “Average (1/9-HPT)” is the average of the inverse (reciprocal) for the mean time of the two trials on the right hand and reciprocal of the mean time of the two left-hand trials from the test patient, Baseline Mean (1/9-HPT) and Std Dev (1/9-HPT) are the baseline values from each patient in all study groups combined at the baseline assessment;

“Average 25-Foot Walk” is the mean time from the two trials of the 25-foot timed walk; and we take the negative value of the Z-score to make the direction of change the same as the other components. Similarly, the Baseline Mean and Std Dev 25-Foot Walk are of all Baseline Groups combined;

and “SDMT” is the score from the test patient, and the Baseline Mean SDMT and Std Dev SDMT of the combined baseline assessments.

If a participant could not use one hand at the outset and could use it subsequently, a baseline value of the worst occurring 9HPT in the same either dominant or nondominant arm will be used to impute the baseline value.

A similar approach is used for second composite with all 4 elements of the MSFC.

9.7. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

The EE population will be defined based upon doses administered and compliance to protocol to determine whether a subset of the 20 subjects may be analyzed as the EE population, to better evaluate efficacy of NurOwn in progressive MS.

10. REFERENCES

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SAP APPENDIX I

DATE: 16 MARCH 2021

STUDY DRUG: NurOwn®

SPONSOR:

Brainstorm Cell Therapeutics

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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Table of Contents

1. BACKGROUND

This document contains additional details that are prespecified as an Appendix to the BCT-101 US safety and efficacy analyses in the statistical analysis plan finalized on April 12, 2019.

The word Treatment will be used instead of Transplant or Transplantation across all study TFLs since it more closely reflects the mechanism of action of the investigative product. The SAP uses the terms NurOwn® or MSC-NTF. For all Tables and Figures the term NurOwn® will be used to distinguish the investigational product from other types of Mesenchymal Stem Cells. The database have the value of NurOwn which is what is displayed in the listings, if needed.

2. ANALYSIS POPULATIONS

Per SAP section 6.5.3, key efficacy analysis on efficacy evaluable (EE) population will not be performed as the difference between EE and modified intent-to-treat (mITT) population is minimal. Additional sub-populations may be analyzed to explore efficacy in subgroups after the database is locked.

3. STUDY ASSESSMENTS

3.1 Handling of Safety or Efficacy data

- If subject discontinues during study (Early Termination) at any visit, then any collected (safety and efficacy) data under EOS/Visit 7 (Week28) will be re-mapped to nearest scheduled visit as per Schedule of Assessment (SoA). If this visit has data already recorded then data will be remapped to the next visit following this nearest visit. This is applicable for all safety and efficacy analysis.
- No imputations will be performed on missing efficacy or safety data except for visits as defined in the SAP. Sensitivity analyses may be performed with imputations after the database is locked.
- The baseline visit will be defined as the most recent assessment prior to receiving the first treatment at Visit 3 considering scheduled and unscheduled visits.
- Handling of unscheduled visits for Laboratory and Vital Summary by timepoints- In change from baseline (CFB), % CFB and Abnormality analysis by visit tables, data collected at unscheduled visits will not be summarized since there are only 2 subjects with unscheduled visit data at pre-treatment visits and no unscheduled post-treatment.

3.2 Demographic and Baseline Characteristics

- All key efficacy measurements will be summarized at baseline visit.

3.3 Medical History and MS Medical History

- Medical history will be coded using the MedDRA, version 23.1 instead of 21.1 as mentioned in SAP section 7.6.

3.4 Prior and Concomitant Medication

PRIOR AND CONCOMITANT MEDICATIONS

The definition of a prior medication is defined as any medication taken prior to the date of first treatment and either stopped prior to the first treatment or continued after it.

3.5 Missing Start and Stop Dates for Adverse Events and Concomitant Medications

The following imputation rule will be used in this study in addition to SAP mentioned in section 6.8.1

- For Start Date: If Day and Year is present but Month is missing then impute January as month.

3.6 Study Drug Exposure and Compliance

- **Additional analysis**
  1. Descriptive statistics summary for duration between treatments 1-2, 2-3 and 1-3.
  2. Summary of number and % of subjects with durations between treatments 1-2 and 2-3 for below categories.
     a. ≤30 days before 8 weeks
     b. >30 and ≤15 days before 8 weeks
     c. >15 and <5 days before 8 weeks
     d. Within 5 days of 8 weeks
     e. >5 and ≤15 days after 8 weeks
     f. >15 and ≤30 days after 8 weeks
     g. >30 days after 8 weeks
  3. Summary of number and % of subjects who received first, not second study drug and second, not third study drug will be summarized.
  4. Since the study drug is administered in the clinic and only three times no formal definition of compliance will be used. The number of IT administrations is summarized.

4. SAFETY ANALYSES

4.1 Adverse Event

- Adverse Event will be coded using the MedDRA, version 23.1 instead of 21.1 as mentioned in SAP section 8.
- Summary for MS relapse will not be done separately in table/listing due to lack of data.
- As mentioned in section 8 of SAP, Treatment-emergent adverse event (TEAE) is an AE that occurs for the first time after initiation of first treatment or if it had occurred prior to initiation first treatment, it worsens in severity after initiation of first treatment. In current TEAE analysis all AEs with onset date after initiation of first treatment are considered as TEAEs irrespective of severity.

- The AE eCRF page assesses discontinuation from treatment (and not from study) while the End of Study (EoS) eCRF page assesses if a subject was discontinued from the study, hence there may be differences between what is recorded on these eCRF pages.. The disposition Table will display the number of subjects discontinued from study as recorded on the end of study page. No AE Tables will be generated for AEs leading to study discontinuation as this data was not collected in the AE eCRF. A listing will provide AE's from the AE datasets for subjects who discontinued the study based on an AE as recorded in the end of study page
- Certain tables will not be generated since there are too few subjects (example procedure related adverse events etc.). But subjects with these AE criteria's will be summarized in listings.

4.2 Laboratory data

SAP section 8.3 incorrectly stated SI Unit for Uric Acid as mg/dL. The correct SI is μmol/L and will be used.

Lab abnormalities:

For analysis of abnormalities across multiple visits such as shift Tables, the worst value will be considered. Lab data will be tabulated using categorizesbelow:

1. missing data
2. clinically significant low abnormality
3. non-clinically significant low abnormality
4. normal values
5. non-clinically significant high abnormalities
6. high clinically significant abnormalities

4.3 Vital Signs

- Summary of Vital Sign Abnormalities will be presented for weight as per below criteria for LOW and HIGH. If percent change from baseline is a decrease of 10% or more then the result will be considered as LOW abnormality; whereas if percent change from baseline is an increase of 10% or more the result will be considered as a HIGH abnormality; If percent change from baseline is between 10% decrease or 10% increase the results will be considered as NORMAL.

5. EFFICACY ANALYSES

Efficacy data from T25FW and 9HPT is available from the CLIMB registry for matched progressive MS patients. In addition MRI data was also collected from matched patients in the CLIMB registry data. Analysis from the BCT-101 study will compare results with the CLIMB registry data. Since data for patients in the CLIMB registry was collected at only two timepoints 1 to 2 years apart, each patient's outcome data will be adjusted by assuming linear change between the two timepoints to estimate the change at 28 weeks (i.e. by determining the slope or change in outcome per week using the two timepoints and then using baseline value + 28 weeks

times this slope to determine the estimated value at 28 weeks). Since the change may not be linear other functions may also be explored.

5.19-Hole Peg Test (9-HPT)

Dominant and non-dominant hand will be analyzed separately in addition to together as mentioned in SAP section 9.2.

5.2 Multiple Sclerosis Walking Scale (MSWS-12)

The SAP indicated that MSWS-12 would be summarized using raw scores (0-60) as well as scores mapped to a 0-100 scale. Upon further review of the literature it was noted that the data are always presented on a 0-100 scale so no tabulations will be generated on the raw scores. The raw scores will be included in the data listings. MSWS-12 on scores mapped to a 0-100 scale will be summarized for following point improvement- ≥10, ≥15 and ≥20 as is done in various publications.

5.2 Actigraph

Summary and Analysis of Change and % Change from Baseline in Daily Step Count following Timed-25 Foot Walking (T25FW) will be excluded from the analyses as data is not available and this cannot be analyzed.

5.3 MSFC

MSFC-4 score will be derived with LCLA Binocular (both eyes) with 1.25% chart with below formula-
MSFC-4 Score = {(Average (1/9-HPT) - Baseline Mean (1/9-HPT) / Baseline Std Dev (1/9-HPT)+ { - (Average 25-Foot Walk - Baseline Mean 25-Foot Walk) / Baseline Std-Dev 25-Foot Walk}+ (SDMT - Baseline Mean SDMT) / Baseline Std Dev SDMT + (LCLA-Binocular1.25% chart - Baseline Mean LCLA-Binocular1.25% chart) / Baseline Std Dev LCLA-Binocular1.25% chart} / 4.0

5.4 MRI

MRI data will also be analyzed for efficacy. Continuous data will be analyzed as changes from baseline and categorical data by counts and percentages.

6. BIOMARKER ANALYSES

Since Biomarker data by nature tends to be highly skewed, all Biomarker data will be log transformed prior to analyses. In addition to analyses of Biomarkers as detailed in the SAP relationships between Biomarkers and efficacy outcomes or MRI data may also be explored.

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