AN OPEN-LABEL, PILOT STUDY OF DARATUMUMAB SC IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE (DARZAD)

Protocol Number: 54767414ALZ001

Principal Investigator: Marc L. Gordon, MD

Sponsor: Northwell Health

IND #: (pending)

Funding and Study Medication Provided by Janssen Scientific Affairs, LLC

Version Number: 1.1

25 April 2019

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor and funding agency, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

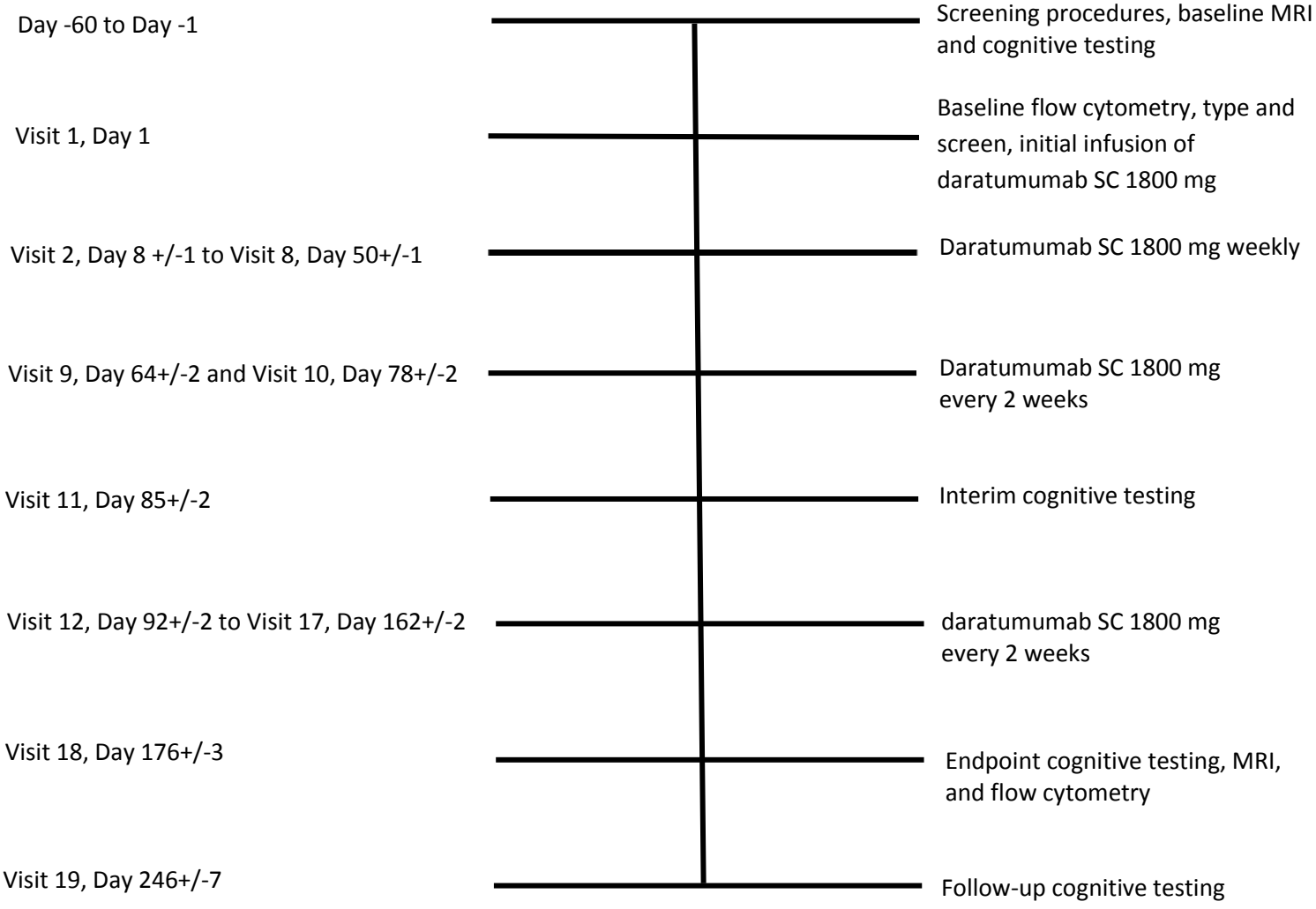
1. PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	An open-label, pilot study of daratumumab SC in patients with mild to moderate Alzheimer's disease
Study Description:	This is an open-label single site pilot study designed to explore whether daratumumab may have a clinically meaningful efficacy signal in patients with mild to moderate Alzheimer's disease.
Objectives:	SPECIFIC AIM: To estimate the proportion of patients with mild to moderate Alzheimer's disease who respond to daratumumab. A patient will be considered a responder if they improve by a minimum of 4 points on the ADAS-cog/11 from baseline at 25 weeks.
Endpoints:	PRIMARY ENDPOINT: Responder rate defined as improvement in standard 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11) score of ≥ 4 points at 25 weeks compared with baseline SECONDARY ENDPOINTS: - The proportion of subjects who are unchanged or improved from baseline at 25 weeks in ADAS-cog/12 score (standard 11 items plus delayed word recall)

	- The proportion of subjects who are unchanged or improved from baseline at 25 weeks in Mini-Mental State Examination (MMSE) score - The proportion of subjects who are unchanged or improved from baseline at 25 weeks in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score - The proportion of subjects who are unchanged or improved from baseline at 25 weeks in AD Composite Score (ADCOMS), a composite score derived from a weighted combination of selected items from the ADAS-cog/12, MMSE, and CDR-SB - The proportion of subjects with treatment-emergent adverse effects - The proportion of subjects with treatment-emergent serious adverse effects TERTIARY/EXPLORATORY ENDPOINTS: - Pattern of change over time at baseline, 12 weeks, 25 weeks, and 36 weeks (12 weeks after completion of treatment) in the following cognitive outcome measures: ADAS-cog/11, ADAS-cog/12, MMSE, CDR-SB, ADCOMS - Change from baseline at 25 weeks in CD38 expression on circulating (whole blood) CD8+ T-cells measured with flow cytometry - Change from baseline at 25 weeks in metabolite ratios [N-acetylaspartate (NAA)/creatine(Cr), myo-inositol (mI)/Cr, choline (Cho)/Cr, and NAA/mI] on single-voxel proton magnetic resonance spectroscopy from the precuneus and posterior cingulate region
Study Population:	Male or female subjects age ≥ 55 to ≤ 85 years with a diagnosis of probable Alzheimer's disease dementia according to National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (McKhann et al. 2011) and a Mini-Mental State Examination (MMSE) score of ≥ 15 and ≤ 26 at the screening visit
Phase:	2a
Description of Sites/Facilities Enrolling Participants:	This is a single-site study being conducted at the Litwin-Zucker Center, Feinstein Institute for Medical Research, 350 Community Drive, 4th floor, Manhasset, NY 11030
Description of Study Intervention:	During the treatment phase, eligible subjects will receive daratumumab SC 1800 mg (daratumumab 1800 mg with rHuPH20 30,000 units) subcutaneous infusion over 3-5 minutes (15 mL) once weekly for 8 weeks followed by daratumumab SC 1800 mg every 2 weeks for 16 weeks.
Study Duration:	24 months
Participant Duration:	Up to 44 weeks (including screening period)

1.2 SCHEMA


Day -60 to Day -1
Screening procedures, baseline MRI and cognitive testing
Visit 1, Day 1
Baseline flow cytometry, type and screen, initial infusion of daratumumab SC 1800 mg
Visit 2, Day 8 +/-1 to Visit 8, Day 50+/-1
Daratumumab SC 1800 mg weekly
Visit 9, Day 64+/-2 and Visit 10, Day 78+/-2
Daratumumab SC 1800 mg every 2 weeks
Visit 11, Day 85+/-2
Interim cognitive testing
Visit 12, Day 92+/-2 to Visit 17, Day 162+/-2
daratumumab SC 1800 mg every 2 weeks
Visit 18, Day 176+/-3
Endpoint cognitive testing, MRI, and flow cytometry
Visit 19, Day 246+/-7
Follow-up cognitive testing

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -60 to -1	Baseline Visit 1, Day 1	Study Visit 2 Day 8 +/-1 day	Study Visit 3 Day 15 +/-1 day	Study Visit 4 Day 22 +/-1 day	Study Visit 5 Day 29 +/-1 day	Study Visit 6 Day 36 +/-1 day	Study Visit 7 Day 43 +/-1 day	Study Visit 8 Day 50 +/-1 day	Study Visit 9 Day 64 +/-2 days	Study Visit 10 Day 78 +/-2 days	Study Visit 11 Day 85 +/-2 days	Study Visit 12 Day 92 +/-2 days	Study Visit 13 Day 106 +/-2 days	Study Visit 14 Day 120 +/-2 days	Study Visit 15 Day 134 +/-2 days	Study Visit 16 Day 148148-2 days	Study Visit 17 Day 162 +/-2 days	Study Visit 18 Day 176 +/-3 days	Final Study Visit 19 Day 246 +/-7 days
Informed consent	X																			
Demographics	X																			
Medical history	X																			
Administer daratumumab SC		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		
Physical and neuro exam	X											X							X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Weight	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
12-lead ECG	X																			
CBC	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Comprehensive metabolic panel	X				X				X		X			X		X		X		X
PT/INR, APTT, TSH, B12 level	X																			
Hepatitis B surface antigen and core antibody	X																			
Hepatitis C Virus antibody	X																			
HIV antigen/antibody screen	X																			
Brain MRI	X																		X	
Amyloid PET scan of brain	X																			
Type and screen		X																		
Flow cytometry		X																	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Modified Hachinski (MHIS)	X																			
GDS	X																			
CDR	X											X							X	X
MMSE	X											X							X	X
ADAS-Cog	X											X							X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Alzheimer's disease (AD) is a gradually progressive neurodegenerative disease that is the leading cause of dementia world-wide. Currently available treatments for AD, which include cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and a low-affinity NMDA receptor antagonist (memantine), have only modest effects on the symptoms of the disease, and do not prevent disease progression. While the underlying cause of Alzheimer's disease remains unknown, there has been extensive evidence that mitochondrial dysfunction (Perez Ortiz and Swerdlow 2019) and neuroinflammation (Heneka et al. 2015) play a significant role in the pathogenesis of AD.

Nicotinamide adenine dinucleotide (NAD) is a co-enzyme found in all living cells. NAD levels decrease during aging and are involved in age-related metabolic decline (Imai and Guarante 2014, Verdin 2015). CD38 is a multi-functional enzyme that hydrolyzes NAD, and is also involved in cell signaling. CD38 levels increase in tissues with age and correlate with NAD decline (Camacho-Pereira et al. 2016) In CD38 knockout mice, tissue levels of NAD are significantly increased (Askoy et al. 2006). When CD38 knockout mice were crossed with APPswePS1ΔE9 transgenic mice to generate Alzheimer's pathology-prone CD38-deficient mice, they exhibited significant reductions in amyloid-beta (Aβ) plaque load and soluble Aβ levels, and this correlated with improved spatial learning. Furthermore, neuronal cultures derived from these mice secreted less Aβ, and this reduction was mimicked when APPswePS1ΔE9 neuronal cultures were treated with inhibitors that blocked CD38 enzyme activity or the signaling pathways controlled by CD38-derived metabolites, suggesting that CD38 may be a novel target for AD treatment (Blacher et al. 2015).

CD38 expression on CD8+ T-cells, indicative of activation, is significantly increased in the blood of early AD patients as compared with age-matched controls, and activated T-cells are capable of trafficking into the central nervous system and exerting cytotoxic effects (Zhang et al. 2013). CD38 significantly affects regulation of the amount and function of activated microglia, with important consequences for injury and repair processes in the brain (Mayo et al. 2008).

2.2 BACKGROUND

Daratumumab is a human IgG1k monoclonal antibody that targets CD38. It is FDA-approved for the treatment of multiple myeloma. Daratumumab has broad-ranging immunomodulatory effects on nonplasma cells that express CD38 (Krejcik et al. 2016). Daratumumab is able to cross the blood-brain barrier (Vercruyssen et al. 2018).

A subcutaneous (SC) formulation of daratumumab with recombinant human hyaluronidase enzyme PH20 (rHuPH20) has been shown to be well tolerated, with low rates of infusion-related reactions and similar efficacy to intravenous (IV) daratumumab in patients with multiple myeloma. (Usmani et al. 2016, Chari et al. 2018). Furthermore, each dose of daratumumab SC can be administered over 3 to 5 minutes, as compared with median first, second, and subsequent IV infusion durations of 7.0, 4.3, and 3.4 hours, respectively.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

While the package insert for the IV formulation of daratumumab (Darzalex) is provided for reference, it should be noted that it includes data for adverse effects in patients with multiple myeloma who were treated with various combination chemotherapy regimens. Furthermore, multiple myeloma is a hematological malignancy that can predispose patients to infection, anemia, thrombocytopenia, and leukopenia. As per the package insert, the safety data reflecting exposure to IV daratumumab 16 mg/kg monotherapy in 156 adult patients with relapsed and refractory multiple myeloma treated in three open-label, clinical trials, with median duration of exposure of 3.3 months (range: 0.03 to 20.04

months), are listed below. Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients. Adverse reactions occurring in at least 10% of patients are presented in Table 1. Table 2 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 1: Adverse reactions with incidence ≥ 10% in patients with multiple myeloma treated with IV daratumumab 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.
[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 2: Treatment-emergent Grade 3-4 laboratory abnormalities (≥ 10 %) in patients with multiple myeloma treated with IV daratumumab 16 mg/kg

	Daratumumab 16 mg/kg (N=156)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions:
In clinical trials of IV daratumumab (monotherapy and combination treatments; N=1166) the incidence of any grade infusion reactions was 40% with the first infusion, 2% with the second infusion, and 4% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions. Grade 4 infusion reactions were reported in 2/1166 (0.2%) of patients.
The median time to onset of a reaction was 1.4 hours (range: 0 to 72.8 hours). The incidence of infusion modification due to reactions was 37%. Median durations of infusion for the 1st, 2nd, and subsequent infusions were 7.0, 4.3, and 3.4 hours respectively. Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

Herpes Zoster Virus Reactivation:
In IV daratumumab monotherapy studies, herpes zoster was reported in 3% of patients.

Hepatitis B Virus Reactivation:
As of 15 November 2018, daratumumab has been administered to approximately 4,407 patients in the setting of clinical trials, with an estimated world-wide post-marketing exposure of 34,316 person-years. HBV reactivation, including fatal cases, has been observed in association with daratumumab. Following a thorough, cross-program review of clinical trial and post-marketing reports, Janssen has determined that HBV reactivation is an important identified risk and adverse drug reaction associated with daratumumab.

Interference with Indirect Antiglobulin Test (indirect Coombs test):
Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognized that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the subject's serum. The determination of a subject's ABO and Rh blood type are not impacted.

Daratumumab SC:
The subcutaneous route of administration for daratumumab was first evaluated by the Janssen Research & Development in Study MMY1004 (PAVO), a Phase 1b, open-label, multicenter, 2-part dose escalation study in patients with relapsed or refractory multiple myeloma. In this ongoing study, daratumumab SC (Dara-SC) is being administered according to the approved monotherapy schedule [i.e., weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until progressive disease (PD) or unacceptable toxicity]. The PAVO study assessed the safety, pharmacokinetics, and efficacy of SC

administration of daratumumab plus rHuPH20 (DARA-PH20). After a median follow-up of 6.5 months (clinical cutoff date of 13 Dec 2017), 25 patients received at least 1 dose of 1800 mg Dara-SC in Study MMY1004. The injection-related reaction rate was 16% and consisted of Grade 1 or 2 chills, dyspnea, sneezing, and allergic rhinitis, and two Grade 3 events of hypertension. None of the injection-related reaction events led to treatment discontinuation. Injection-site reactions occurred in 12% (n=3) of patients, all were Grade 1. The events were discoloration/injection site induration, hematoma, and erythema. The overall response rate (ORR) was 52% with 28% very good partial response rate (VGPR). Median progression-free survival (PFS) has not been reached. The efficacy and adverse event profile are consistent with that of IV daratumumab with a lower rate of injection-related reactions. Based on these clinical data and supported by the pharmacokinetic profile of Dara-SC, the safety and efficacy of Dara-SC appear equivalent to and may be better than Dara-IV. Together these findings suggest that co-formulated SC daratumumab 1800 mg plus rHuPH20 is well tolerated and achieves response rates similar to those observed with daratumumab administered by IV infusion. In addition, the daratumumab SC administration has an added benefit of shorter administration time (3 to 5 minutes for SC daratumumab injection versus a median duration of 7 hours when administered by IV infusion).

Please refer to the Investigator's Brochure (IB) for more detailed safety data about daratumumab.

Known potential risks of concurrent protocol-specific medications:

1. Side effects of dexamethasone may include nausea, vomiting, heartburn, headache, dizziness, trouble sleeping, appetite changes, increased sweating, high blood sugar, mood swings, bleeding from the stomach, swelling of the hands or feet, and bone damage.
2. The most common adverse reactions in adult patients treated with acetaminophen (Tylenol) are nausea, vomiting, headache, and insomnia.
3. Side effects of diphenhydramine (Benadryl) may include sleepiness, confusion, dizziness, incoordination, dry mouth, blurred vision, upset stomach, constipation, and difficulty urinating.
4. The most common adverse reactions to montelukast (incidence >5% and greater than placebo, listed in descending order of frequency) are upper respiratory infection, fever, headache, pharyngitis (sore throat), cough, abdominal pain, diarrhea, otitis media (ear infection), influenza, rhinorrhea (runny nose), and sinusitis (inflammation of sinuses).
5. Side effects of acyclovir may include nausea, vomiting, dizziness, diarrhea, sleepiness, and confusion.

2.3.2 KNOWN POTENTIAL BENEFITS

While daratumumab is FDA-approved for the treatment of multiple myeloma, and is under study for the treatment of other hematological malignancies, it has not previously been studied for the treatment of Alzheimer's disease. There is a rationale to suggest a potential for direct benefit to AD subjects. However, this study is exploratory, and there is no guarantee of direct benefit. The results of this study may provide generalizable knowledge about the potential utility of this strategy for the treatment of Alzheimer's disease, and should provide more specific data regarding the benefit-risk ratio of daratumumab in this patient population.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

As there are no currently available disease-modifying treatments for AD, there is an adequate rationale to explore the potential efficacy of daratumumab in this small open-label study. The safety profile of daratumumab has been well-characterized in patients with multiple myeloma. Since the AD subjects to be enrolled in this study will be otherwise healthy, without history or evidence of malignancy, cardiac, pulmonary, or other significant medical illnesses or laboratory abnormalities, we expect the risk of adverse hematological effects or infectious complications to be lower than in patients with multiple myeloma. In view of the potential for daratumumab to interfere with the Indirect Antiglobulin Test (indirect Coombs test), and mask detection of antibodies to minor antigens in the subject's serum, type and screen will be sent prior to treatment initiation. To minimize the risk of post-infusion reactions, individuals with a history of asthma or chronic obstructive pulmonary disease will be excluded, and subjects will be premedicated with montelukast 10 mg orally 1 to 3 hours prior to the first dose of daratumumab, diphenhydramine 25 mg orally 1 to 3 hours prior to each dose, acetaminophen 1000 mg orally 1 to 3 hours prior to each dose, and dexamethasone 20 mg orally 1 to 3 hours prior to the first 3 doses, 10 mg orally 1 to 3 hours prior to all subsequent doses, and 4 mg orally the day after each dose. To avoid hepatitis B virus reactivation, subjects with serologic evidence of current or prior hepatitis B infection will be excluded. To prevent herpes zoster reactivation, patients will also be treated with oral acyclovir 400 mg daily beginning the day after the first dose and continuing until 12 weeks after the final dose. After the first dose, subjects will have a CBC performed within 48 hours prior to each subsequent infusion, and the scheduled infusion will be held if there is evidence of clinically significant anemia, neutropenia, leukopenia, or thrombocytopenia. Additional safety laboratory monitoring will include a comprehensive metabolic panel (CMP) every 4 weeks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To estimate the proportion of patients with Alzheimer's disease who have a clinically meaningful response to daratumumab	Responder rate defined as improvement in standard 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11) score of ≥ 4 points at 25 weeks compared with baseline	An improvement of ≥ 4 points in ADAS-cog/11 score has been deemed to be clinically meaningful. Based on previous results in patients with mild to moderate AD maintained on stable treatment with a cholinesterase inhibitor, the expected responder rate at 25 weeks (defined as improvement in ADAS-

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		cog/11 score of ≥ 4 points) is 20% (0.20).
Secondary		
To estimate the proportion of patients who remain stable (unchanged) or improve at 25 weeks vs baseline on additional cognitive outcome measures	The proportion of subjects who are unchanged or improved from baseline to 25 weeks in ADAS-cog/12 score (standard 11 items plus delayed word recall) The proportion of subjects who are unchanged or improved from baseline to 25 weeks in Mini Mental State Examination (MMSE) score The proportion of subjects who are unchanged or improved from baseline to 25 weeks in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score The proportion of subjects who are unchanged or improved from baseline to 25 weeks in ADCOMS score (a composite score derived from a weighted combination of selected items from the ADAS-cog/12, MMSE, and CDR-SB)	These are other widely used cognitive outcome measures in clinical trials of patients with Alzheimer's disease
To estimate the proportion of subjects with treatment-emergent adverse effects and severe adverse effects	The proportion of subjects with one or more treatment-emergent adverse events The proportion of subjects with one or more treatment-emergent serious adverse events	To describe the adverse event profile of subcutaneous daratumumab in patients with mild to moderate Alzheimer's disease
Tertiary/Exploratory		
To describe the pattern of change over time in response to daratumumab on cognitive outcome measures	Change over time at baseline, 12 weeks, 25 weeks, and 36 weeks (12 weeks after completion of treatment) in the following cognitive outcome measures: ADAS-cog/11, ADAS-cog/12, MMSE, CDR-SB, ADCOMS	To observe the time to onset and persistence of cognitive responses to daratumumab

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To measure the effects of daratumumab on CD38 expression in circulating $CD8^+$ T-cells	Change from baseline to 25 weeks in CD38 expression on circulating (whole blood) $CD8^+$ T-cells measured with flow cytometry	To provide evidence of target engagement for the putative immunological mechanism of action
To explore the effects of daratumumab on cerebral metabolites.	Change from baseline to 25 weeks in metabolite ratios (N-acetylaspartate/creatine, myo-inositol/creatine, choline/creatine, and N-acetylaspartate/myo-inositol) on single-voxel protein magnetic resonance spectroscopy from the precuneus and posterior cingulate region	To provide evidence of daratumumab effects on cerebral metabolism

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label single site pilot study designed to explore whether daratumumab may have a clinically meaningful efficacy signal in patients with mild to moderate Alzheimer's disease. During the treatment phase, eligible subjects will receive daratumumab SC 1800 mg (daratumumab 1800 mg with rHuPH20 30,000 units) subcutaneous infusion over 3-5 minutes (15 mL) once weekly for 8 weeks followed by daratumumab SC 1800 mg every 2 weeks for 16 weeks. The primary endpoint is responder rate defined as improvement in standard 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog/11) score of ≥ 4 points at 25 weeks compared with baseline.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a pilot study, the purpose of which is explore whether there is a clinically meaningful efficacy signal for daratumumab in patients with mild to moderate Alzheimer's disease. The proposed sample size of 15 patients is based on feasibility and availability of resources, and not on a formal power calculation.

4.3 JUSTIFICATION FOR DOSE

The dosing regimen for this study is based on prior studies in patients with multiple myeloma, since the safety profile of that regimen has been well-established. We are using the SC formulation of daratumumab because it is associated with substantially lower risk of post-infusion reactions, much shorter administration times, and greater convenience for the subjects.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA for all subjects enrolled in the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Each subject must be ≥ 55 to ≤ 85 years of age at the screening visit.
2. Each subject must have a diagnosis of probable AD dementia according to National Institute on Aging-Alzheimer's Association (NIA-AA) criteria.
3. Each subject must have a Mini-Mental State Examination (MMSE) score ≥ 15 and ≤ 26 at the screening visit.
4. Each subject must have a Magnetic Resonance Imaging (MRI) scan performed during the screening period that is consistent with a diagnosis of AD.
5. Each subject must have a positive amyloid Positron Emission Tomography (PET) scan, either performed during the screening period, or previously performed provided that the scan and result are considered acceptable by the investigator.
6. If the subject is receiving a cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) and/or memantine, the dose must have been stable for at least 12 weeks before the screening visit, and the subject must be willing to remain on the same dose for the duration of the trial.
7. Each subject must have a study partner who is reliable and competent. The study partner must have a close relationship with the subject, have face to face contact at least 3 days/week for a minimum of 6 waking hours/week, and be willing to accompany the subject to all required study visits.
8. Each subject must have no clinically significant abnormal laboratory test results [complete blood count (CBC), prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (APTT), comprehensive metabolic panel (CMP), thyroid stimulating hormone (TSH), and vitamin B12 level] at the screening visit.
9. Each subject must have results of a physical and neurological examination and vital signs within normal limits or clinically acceptable to the investigator at the screening visit.

10. If female, the subject must be postmenopausal defined as: No menses for 12 or more months without an alternative medical cause OR permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. The subject has a Rosen-modified Hachinski Ischemia Score > 4 at the screening visit.
2. The subject has a known history of stroke or evidence from screening MRI that is clinically significant in the investigator's opinion.
3. The subject has evidence of a clinically relevant neurological disorder other than probable AD at the screening visit, including: vascular dementia, Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, mental retardation, hypoxic cerebral damage, or head trauma with loss of consciousness that led to persistent cognitive deficits.
4. The subject has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-5 criteria, including schizophrenia or other psychotic disorder, bipolar disorder, delirium, or major depression. (Major depression in remission is not exclusionary.) A score on the 15-item Geriatric Depression Scale (GDS) of 5 or more requires an assessment by an appropriate health care professional to evaluate for the presence of major depression. Subjects with a score of 5 or more who are not diagnosed with major depression following such an assessment may be included in the trial.
5. The subject has a history of alcoholism or drug dependency/abuse within the last 5 years before screening.
6. The subject has been treated with any investigational product within 60 days or 5 half-lives (whichever is longer) prior to the screening visit.
7. The subject has been treated with anti-amyloid-beta or anti-tau protein monoclonal antibodies within one year prior to the screening visit.
8. The subject has been treated with an active vaccine targeting amyloid-beta or tau protein.
9. The subject has received a live/live-attenuated bacterial or viral vaccine within 3 months prior to the screening visit.
10. The subject has been treated with immunosuppressive medications, such as azathioprine, cyclosporine, methotrexate, tacrolimus, or mycophenylate, within 2 months prior to the screening visit.
11. The subject has been treated with a course of corticosteroids longer than 5 days within 2 months prior to the screening visit.
12. The subject is taking or is anticipated to require treatment with estrogens.
13. The subject is taking or is anticipated to require treatment with an anticoagulant medication, including warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, or enoxaparin.
14. The subject is taking or is anticipated to require treatment with aspirin at a dose higher than 325 mg daily.
15. The subject has a history of asthma or chronic obstructive pulmonary disease.

16. The subject has had a myocardial infarction, unstable angina, stroke, transient ischemic attack or required intervention for any of these conditions (e.g., coronary artery bypass graft, percutaneous coronary intervention via cardiac catheterization, thrombolytic therapy) within 6 months prior to the screening visit.
17. The subject has had an infection requiring medical intervention within 30 days prior to the screening visit.
18. The subject has serologic evidence of current or prior hepatitis B virus (HBV) infection based on hepatitis B surface antigen or hepatitis core antibody blood tests at the screening visit.
19. The subject has serologic evidence of hepatitis C virus (HCV) infection based on hepatitis C antibody blood test at the screening visit.
20. The subject has serologic evidence of human immunodeficiency virus (HIV) infection based on HIV antigen/antibody test at the screening visit.
21. The subject has a platelet count less than 50,000 per microliter (mL) at the screening visit.
22. The subject has a creatinine clearance less than 30 mL/minute at the screening visit.
23. The subject has a history or evidence of a malignancy (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or localized prostate carcinoma) within the 2 years prior to the screening visit.
24. The subject has had any other unstable/uncontrolled medical illness within 12 weeks prior to the screening visit such that, in the judgment of the investigator, participation in the trial would pose a significant medical risk to the subject.
25. The subject has significant visual or auditory impairment, or limited English proficiency, that in the investigator's opinion would preclude collection of outcome measures.
26. The subject has any contraindication to or inability to tolerate brain MRIs (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
27. The subject has any contraindication to or inability to tolerate a PET scan (includes current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject in any given year would exceed acceptable limits of annual and total dose).
28. The subject has a history of allergy to dexamethasone, diphenhydramine, acetaminophen, montelukast, or acyclovir.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to abstain from alcohol for 24 hours before the start of each dosing or cognitive assessment visit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an MMSE score above the cutoff of 26 may be rescreened after an interval of at least 3 months. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from our internal database of subjects previously evaluated at the Litwin-Zucker Research Center who have indicated that they are willing to be contacted about future studies. We will also screen subjects who are referred by other providers within Northwell Health Physician Partners or by community physicians. We anticipate accrual of 15 subjects over an 18-month enrollment period. Due to the inherent nature of the study population, with cognitive impairment due to Alzheimer's disease, it is anticipated that many of these subjects will lack decisional capacity to provide informed consent. Accordingly, all potential subjects will be assessed for capacity to provide informed consent by one of the study physicians, who are either neurologists or geriatric psychiatrists with extensive experience in assessing decisional capacity. If a subject is determined to lack capacity to provide informed consent, surrogate consent will need to be obtained from a legally authorized representative. In that instance, the subject will also need to provide assent to participate in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Daratumumab, a CD38 antagonist, is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38 expressing cells with high affinity. The subcutaneous formulation is administered in combination with recombinant human hyaluronidase (rHuPH20) to facilitate fluid dispersion.

6.1.2 DOSING AND ADMINISTRATION

During the treatment phase, eligible subjects will receive daratumumab SC 1800 mg (daratumumab 1800 mg with rHuPH20 30,000 units) given through a syringe and needle by a manual push over approximately 3 to 5 minutes once weekly for 8 weeks followed by daratumumab SC 1800 mg every 2 weeks for 16 weeks. Doses will be administered at alternating locations on the abdomen. The volume of 1800 mg Daratumumab for SC injection will be approximately 15 mL. In case of significant discomfort during manual injection, a slower injection speed may be used or alternatively the total dose may be given in 2 separate locations.

6.1.3 CONCURRENT PROTOCOL-SPECIFIC MEDICATIONS

To minimize the risk of post-injection reactions, subjects will be premedicated with montelukast 10 mg orally 1 to 3 hours prior to the first dose of daratumumab, diphenhydramine 25 mg orally 1 to 3 hours prior to each dose, acetaminophen 1000 mg orally 1 to 3 hours prior to each dose, and dexamethasone 20 mg orally 1 to 3 hours prior to the first 3 doses, 10 mg orally 1 to 3 hours prior to all subsequent doses, and 4 mg daily orally the day after each dose. To prevent herpes zoster reactivation, patients will also be treated with oral acyclovir 400 mg daily beginning the day after the first dose and continuing until 12 weeks after the final dose.

6.1.4 MANAGEMENT OF LOCAL INJECTION SITE REACTIONS

Local injection site reactions, such as induration and erythema have been observed following SC administration of daratumumab in abdominal SC tissue. The reactions usually resolve within 60 minutes. Local injection site reactions can be managed conservatively with cold compresses as need.

6.1.5 MANAGEMENT OF SYSTEMIC INJECTION-RELATED REACTIONS

Patients should be carefully observed during daratumumab administration. If an injection-related reaction develops, then daratumumab administration should be temporarily interrupted.

Patients who experience adverse events during daratumumab administration must be treated for their symptoms:
• Treatment with acetaminophen, antihistamine, or corticosteroids, may be administered as needed.
• IV saline may be indicated.
• For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids, or bronchodilators.
• For hypotension, patients may require vasopressors.

In the event of a life-threatening reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, the patient will be transported to the Emergency Room. Daratumumab should be discontinued, no additional daratumumab should be administered to the patient, and the patient must be permanently withdrawn from daratumumab treatment.

Injection-related Reactions of Grade 1 or Grade 2:
If the investigator assesses a Grade 1 to 2 injection-related adverse event to be related to daratumumab, then administration of daratumumab should be paused. When the patient's condition is stable, daratumumab administration may be resumed at the investigator's discretion.

If the patient experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the patient must be permanently withdrawn from daratumumab treatment.

Injection-related Reactions of Grade 3 or Higher:
For injection-related reactions (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped, and the patient must be observed carefully until

resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. If the intensity of the event returns to Grade 3 after restart of the daratumumab administration, then the patient must be permanently discontinued from daratumumab treatment.

For injection-related adverse events that are Grade 4, the daratumumab administration must be stopped, and the patient permanently discontinued from daratumumab treatment.

Recurrent Injection-related Reactions:
If a Grade 3 injection-related reaction (or Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent daratumumab administration, the subject must be permanently discontinued from daratumumab treatment.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Daratumumab SC will be supplied by Janssen Scientific Affairs, LLC through the drug distribution vendor CSM (Clinical Supplies Management Holdings, INC). A drug template request form will be sent to the central drug ordering mailbox. During the course of the study, the site will ensure drug inventory is checked on a regular basis and enough lead time is given to order, process, and ship drug to the site.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Daratumumab SC drug product is a colorless to yellow liquid. Daratumumab SC drug product is co-formulated at a concentration of 120 mg/mL daratumumab with 2000 U/mL rHuPH20 in an isotonic buffer consisting of histidine, sorbitol, methionine, NaCl and polysorbate 20 at pH 5.6. Daratumumab SC drug product is supplied as a single-use, sterile, liquid product in a glass vial with stopper and aluminum seal with gray plastic flip-off cap.

6.2.3 PRODUCT STORAGE AND STABILITY

The daratumumab vials should be stored in the original carton in a refrigerator at 2˚C to 8˚C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Since daratumumab does not contain preservatives, any unused portion remaining in the vial must be discarded.

6.2.4 PREPARATION

1. Check the vial to ensure that the vial is labeled for Subcutaneous Administration.
2. Inspect the expiration date on the carton label before withdrawing the drug from vial to syringe.
3. After removal of the vial from 2-8˚C storage, equilibrate at room temperature (RT) for at least 30 minutes.

4. The vial must not be stored at room temperature and room light for more than 24 hours cumulative hold (including equilibration time before first vial puncture).
5. The maximum time at room temperature and room light from vial puncture to administration to the subject is 4 hours.
6. Remove cap and clean top of vial with alcohol wipe.
7. Gently swirl the vial (do not shake). Inspect the vial for any visible particles. Drug product (DP) solution should be colorless to yellow. Do not use the solution if it contains large number of white, clear or translucent particles or if it contains dark opaque particles.
8. Attach disk filter, spike filter or filter needle to the barrel of 20 mL sterile syringe.
9. Withdraw the entire contents of the RT equilibrated vial through the disk filter, spike filter or filter needle.
10. If a filter becomes clogged or leaking is observed, obtain a new vial and a new filter, and re-start the withdrawal process into a new syringe.
11. Some bubbles/foaming may be observed upon filtration. This is normal and does not affect DP quality. If multiple small bubbles/foaming are observed, let the syringe rest for 1 or 2 minutes to let the bubbles/foam dissipate. If a small amount of large air bubbles is observed, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe.
12. Remove and discard the disk filter and transfer needle, mini-spike, or filter needle.
13. If air bubbles were previously observed, slowly push the plunger up to force the air bubbles out of the syringe.
14. Check the volume in the syringe.
15. Upon filtration and after removal of air, the syringe must contain at least 15.5 mL.
16. If it is not possible to adjust to 15.5 mL, a second vial of daratumumab SC 1800 mg DP must be allowed to equilibrate at ambient room temperature for at least 30 minutes prior to withdrawal and a new filter and a new transfer needle must be used for filtration of the second vial of DP into the same syringe (with the previously filtered DP).
17. A winged infusion set or a syringe tip cap should be attached at this time.
18. The winged infusion set attached can be adjusted to final dose of 15 mL at this time point. Alternatively (if a syringe tip cap is used), adjustment for the final dose can be accomplished in the patient care area.

6.2.5 ADMINISTRATION

1. Remind the patient that they should try to remain still during the procedure and to inform the Health Care Provider (HCP) if they are uncomfortable.
2. Check the label on the prepared syringe to confirm that the drug has not passed the expiration time and date.
3. Inspect the syringe for any visible particles: Drug product solution should be colorless to yellow. Do not use the solution if it contains large number of white, clear or translucent particles or if it contains dark opaque particles.
4. Ensure the intended dose is available in the syringe: A) If the syringe was delivered with a syringe tip cap: remove the syringe tip cap and attach a winged infusion set and adjust to 15mL DP in the

syringe. B) If the syringe was delivered with a winged infusion set: remove needle cap from the winged infusion set and confirm that 15mL are present in the syringe.
5. Select a site for SC injection: abdomen only, ~ 3 inch (7.5 cm) to the right or left side of the navel.
6. Cleanse the area (~ 2 inch or 5 cm) around the site with alcohol wipe.
7. Pinch a 2-inch (5 cm) fold of the cleaned skin at the targeted SC injection site between the thumb and index finger and hold firmly.
8. Hold the winged infusion set by the wings. Insert the needle at a 45-degree angle.
9. Release pinch after the needle is inserted.
10. Hold the syringe with one hand. With the other, pull back the plunger slightly to check for blood to make sure that a blood vessel has not been punctured.
11. Use one hand to push the plunger rod and another hand to hold the winged infusion set for stability during injection.
12. Deliver the dose by manual injection over approximately 3 to 5 minutes. Try to maintain a constant rate during injection.
13. Check for leakage during administration and monitor the injection site.
14. If healthcare provider (HCP) feels arm fatigue, delivery may be paused. If the patient is experiencing pain the rate of the injection may be slowed down.
15. If the patient is experiencing pain or significant discomfort that is not alleviated by slowing down, the injection a second injection site may be chosen on the opposite side of the abdomen (left or right of navel). Additional site preparations and needle safety precautions are required.
16. Remove the needle from the skin. Do not flush the winged infusion set. Do not press or rub the site of injection.
17. Immediately place the syringe and needle component into a disposal container.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable. (This is an open-label study.)

6.4 STUDY INTERVENTION COMPLIANCE

Not applicable. (All doses of the study medication will be administered at the Research Center.)

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

As per the inclusion criteria, if the subject is receiving a cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) and/or memantine, the dose must have been stable for at least 12 weeks before the screening visit, and the subject should remain on the same dose for the duration of the trial. As per the exclusion criteria, prohibited medications include any investigational product within 60 days or 5 half-lives (whichever is longer) prior to the screening visit or anti-amyloid-beta or anti-tau protein monoclonal antibodies within one year prior to the screening visit, and for the duration of the trial. To

minimize the risk of injection site hematomas, anticoagulant medications, including warfarin, dabigatran, rivaroxaban, apixaban, edoxaban, heparin, or enoxaparin, are also prohibited throughout the treatment phase of the study (through Visit 17). Live/live-attenuated bacterial or viral vaccines are prohibited from 3 months prior to the screening visit and throughout the treatment phase of the study (through Visit 17). This includes oral typhoid, oral cholera, measles, mumps, rubella, oral polio (Sabin), yellow fever, varicella (Varivax or Zostavax), rotavirus, Japanese encephalitis, or live-attenuated influenza (FluMist) vaccines. Treatment with immunosuppressive medications, such as azathioprine, cyclosporine, methotrexate, tacrolimus, or mycophenylate, is prohibited from 2 months prior to the screening visit and throughout the treatment phase of the study (through Visit 17). Treatment with courses of corticosteroids longer than 5 days are prohibited from 2 months prior to the screening visit and throughout the treatment phase of the study (through Visit 17). Due to potential interactions with rHuPH20 that could slow absorption of study medication, treatment with estrogens, or aspirin at a dose higher than 325 mg daily, is prohibited throughout the treatment phase of the study (through Visit 17). Medications that could have adverse effects on cognition, including opioid analgesics, centrally acting anticholinergic medications, sedative/hypnotic medications, and benzodiazepines, are not to be used within 72 hours prior to cognitive testing (at Screening, Visit 11, Visit 18, and Visit 19).

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Dose Delays and Dose Modifications:
Individual dose modification of daratumumab is not permitted, but dose delay is recommended as the primary method for managing daratumumab-related toxicities.

Daratumumab-Related Toxicity Management:
If any of the following criteria are met and the toxicity is more than expected daratumumab injection must be held to allow for recovery from toxicity. If attribution is unclear, then daratumumab should be held until recovery from toxicity as noted below.

The criteria for a dose delay are:

- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If daratumumab administration does not commence within the prespecified window of the scheduled administration date (Table 3), then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

Table 3:Daratumumab-related Toxicity Management

Daratumumab Dosing Frequency	**Dose Missed**	**Dosing Resumption**
Weekly	>3 days	Next planned weekly dosing date
Every 2 weeks	>7 days	Next planned every-2-weeks dosing date

Interruption or discontinuation from daratumumab SC infusions does not mean discontinuation from the study, and subjects will be asked to return for scheduled assessments as per the protocol at Visit 11, Visit 18, and Visit 19, if not already completed. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. Significant study intervention non-compliance
2. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
3. If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

1. The site will attempt to contact the participant and reschedule the missed visit if feasible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
2. Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
3. Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog): The ADAS-Cog is the most widely used cognitive scale in AD clinical studies. The standard 11-item version (ADAS-Cog/11) includes both subject-completed tests and observer-based assessments. Specific tasks include Word Recall, Naming Objects and Fingers, Commands, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition, and Language. The score ranges from 0 to 70 with each point representing a performance error and higher scores reflecting worse performance (Rosen et al. 1984). An improvement (decrease) of ≥ 4 points in ADAS-cog/11 score has been deemed to be clinically meaningful (Raina et al. 2008). The 12-item version (ADAS-Cog/12) adds a delayed word recall task, scored from 0 to 10. The ADAS-Cog/12 score is the total of the ADAS-Cog/11 plus the delayed recall score, and therefore has a range of 0 to 80 (Sano et al. 2011). The ADAS-Cog will be administered at the Screening Visit, Visit 11, Day 85+/-2, Visit 18, Day 176+/-3, and Visit 19, Day 246+/-7.

Clinical Dementia Rating Scale Sum of Boxes (CDR-SB): The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual (Hughes et al. 1982). The CDR-SB has been proposed as an acceptable approach for following disease progression and confirming treatment in AD (Lynch et al. 2006). The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18, with higher scores indicating more impairment. The CDR will be administered at the Screening Visit, Visit 11, Day 85+/-2, Visit 18, Day 176+/-3, and Visit 19, Day 246+/-7.

Mini Mental State Examination (MMSE): The MMSE is a 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing (Folstein et al. 1975). Scores range from 0 (most impaired) to 30 (no impairment). The MMSE will be administered at the Screening Visit, Visit 11, Day 85+/-2, Visit 18, Day 176+/-3, and Visit 19, Day 246+/-7.

AD Composite Score (ADCOMS): The ADCOMS is a composite score derived from a weighted combination of selected items from the ADAS-cog/12, MMSE, and CDR-SB. The range of the ADCOMS is between 0 and 1.97. A higher score is indicative of greater impairment. Items contributing to the ADCOMS include 4 items of the ADAS-cog, two items of the MMSE (scored in reverse, as item maximum score minus measured score), and all six items of the CDR-SB (Wang et al. 2016).

8.2 SAFETY AND OTHER ASSESSMENTS

Demographics: Subject demographic information will be collected at the Screening Visit, including date of birth (or age), sex, race/ethnicity, native language, and highest education level.

Medical history: Medical and surgical history, prior and concurrent medications including cholinesterase inhibitor and memantine use, and current medical conditions will be recorded at the Screening Visit. Medical history will include history of cognitive impairment and psychiatric history.

Height and weight: Height will be measured at the Screening Visit. Weight will be measured at every visit except Visit 11 (the interim cognitive testing visit).

Vital signs: Temperature, blood pressure, heart rate, and respiratory rate will be assessed at the Screening Visit, prior to every infusion, 1 hour and 2 hours after the first infusion (Visit 1), 1 hour after every subsequent infusion (Visits 2 through 10 and 12 through 17), and at Visits 11, 18, and 19.

Physical and neurological examination: Physical and neurological examination will be performed by a study physician at the Screening Visit, Visit 11, Visit 18, and Visit 19.

Modified Hachinski Ischemia Score (MHIS): The Rosen-Modified Hachinski Ischemia Score (MHIS) is a tool to identify the possibility of a vascular etiology for a subject's cognitive impairment (Rosen et al. 1980). It will be performed by a study physician at the Screening Visit.

Geriatric Depression Scale (GDS): The Geriatric Depression Scale (GDS) (15 point version) is a screening assessment tool for depression specifically designed for older people (Sheikh and Yesavage 1986). A score of 5 or higher is suggestive of depression. It will be performed at the Screening Visit.

Electrocardiogram (ECG): 12-lead ECG will be obtained for screening purposes only at the Screening Visit.

Blood tests: Blood tests to be collected at the Screening Visit will include complete blood count (CBC), comprehensive metabolic panel (CMP), prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (APTT), thyroid-stimulating hormone (TSH), vitamin B12 level, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus antibody (HCVAb), and human immunodeficiency virus antigen/antibody screen (HIVAg/Ab). Blood samples will be obtained at Visit 1, prior to the first infusion, for type and screen and flow cytometry. After the first dose, subjects will have a CBC performed within 48 hours prior to each subsequent infusion (Visits 2 through 10 and 12 through 17). Additional safety laboratory monitoring will include a CMP every 4

weeks (Visits 4, 8, 10, 13, 15, and 17). CBC and CMP will also be obtained 12 weeks after the final dose (Visit 19).

Brain MRI: Brain MRI will be performed within the screening period and at Visit 18. MRI acquisition will be performed on a 3T MRI scanner (Siemens MAGNETOM Prisma). The sequences obtained will include proton magnetic resonance spectroscopy (^{1}H-MRS) from a mid-sagittal oblique 10.8 cm^3 (2 × 2 × 2.7 cm) voxel in the region of the precuneus and posterior cingulate cortex.

Amyloid PET scan of brain: An amyloid PET scan may be performed within the screening period to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used provided that the scan and result are considered acceptable by the investigator.

Concomitant medications: Concomitant medications will be recorded at the Screening Visit and reviewed and updated at Visits 1-19.

Adverse events review: Subjects and study partners will be asked about adverse events at Visits 1-19. Adverse events will also be assessed if they are reported at any other time during the study by the subject or study partner, in person or by telephone.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. [Definition per International Conference on Harmonisation (ICH)]

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important**

*Life-Threatening Conditions:
Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

**Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious. NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

8.3.2.1 HOSPITALIZATION

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities. [Equivalent to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1]

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. [Equivalent to NCI CTCAE Grade 2]
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. [Equivalent to NCI CTCAE Grade 3 or higher] Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For daratumumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator or study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the study staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Maintenance of Safety Information:
All safety data should be maintained in a clinical database in a retrievable format. The Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

8.3.5 ADVERSE EVENT REPORTING

All adverse events (AEs) will be recorded in the Case Report Form (CRF), and will be reviewed on an ongoing basis by the investigator and the Independent safety monitor. The Principal Investigator shall

be solely responsible for complying, within the required timelines, with any safety reporting obligation to competent Health Authorities and the IRB, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies. The Principal Investigator will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section. This study has been designated as an interventional study. As such, all adverse events for Janssen Medicinal Products regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug. For the purposes of this study, the Janssen medicinal product is daratumumab. Nonserious AEs will be reported to Janssen Scientific Affairs, LLC on an annual basis. Timetables for reporting serious adverse events, events of special interest, pregnancy, and product quality complaints are detailed in the relevant sections below.

The Principal Investigator will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with the Transmission Methods described below, in English within 24-hours of becoming aware of the event(s).

Transmission Methods:
The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
  - Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

Dissemination of Safety Information from Janssen to Institution/Principal Investigator:
The Principal Investigator will be responsible for submitting IND safety reports for the Study Product to the Institution's IRB in accordance with Federal regulations 21 CFR 312.66.

Janssen Scientific Affairs, LLC agrees to provide to the Principal Investigator IND safety reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the Principal Investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to Janssen Scientific Affairs, LLC any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or Investigator's Brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by Janssen Scientific Affairs, LLC and should be provided as soon as possible.

The Institution/Principal Investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Institution/Principal Investigator's initial receipt of the information. In addition, the Institution/Principal Investigator must notify the FDA in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Institution/Principal Investigator determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Subjects and study partners will be informed of any clinically significant incidental findings on laboratory testing or imaging studies. With appropriate written authorization from the subject or their legally authorized representative, those results can be communicated to the subject's treating physician(s). A summary of the aggregate results of the study will be provided to study participants after data analysis is complete, and will be posted on the ClinicalTrials.gov website.

8.3.8 EVENTS OF SPECIAL INTEREST

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if nonserious). These adverse events are:

- Infusion reactions: ≥ Grade 3
- Infections: ≥ Grade 4
- Cytopenias: ≥ Grade 4
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis – all Grades

Any Adverse Event of Special Interest that is to be reported to Janssen Scientific Affairs, LLC should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC within 24 hours of knowledge of the event.

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of the event.

8.3.9 REPORTING OF PREGNANCY

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the Principal Investigator within 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Principal Investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.10 REPORTING OF PRODUCT QUALITY COMPLAINTS (PQC)

A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage

or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but are not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the Principal Investigator within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or nonserious adverse event, the Principal Investigator must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the Independent Safety Monitor as soon as possible, but within 5 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Independent Safety Monitor as soon as possible, but within 5 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and the Office of the Human Research Protections (OHRP). The OHRP Director ensures that all steps of this process are completed within 30 days of the IRB decision. For more serious actions, the OHRP Director will expedite reporting. All correspondence with any federal agency will be sent on behalf and with knowledge of the Institutional Official.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Subjects, study partners, and legally authorized representatives will be informed of any UPs that might affect their willingness to continue participation in the study. If the UP requires modification of the informed consent form, active subjects will be re-consented.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

SPECIFIC AIM: To estimate the proportion of patients with Alzheimer's disease who respond to daratumumab.

OUTCOME VARIABLE: A patient will be considered a responder if they improve by a minimum of 4 points on the ADAS-cog/11 from baseline at 25 weeks.

STATISTICAL METHODS: The proportion of patients who respond to daratumumab will be estimated, and the associated 95% exact binomial confidence interval will be calculated.

- Primary Efficacy Endpoint:

- Responder rate defined as improvement in standard 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11) score of ≥ 4 points at 25 weeks compared with baseline

- Secondary Efficacy Endpoints:

- The proportion of subjects who are unchanged or improved from baseline at 25 weeks in ADAS-cog/12 score (standard 11 items plus delayed word recall)

- The proportion of subjects who are unchanged or improved from baseline at 25 weeks in Mini Mental State Examination (MMSE) score

- The proportion of subjects who are unchanged or improved from baseline at 25 weeks in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score

- The proportion of subjects who are unchanged or improved from baseline at 25 weeks in ADCOMS score (a composite score derived from a weighted combination of selected items from the ADAS-cog/12, MMSE, and CDR-SB)

- Secondary Safety Endpoints:

- The proportion of subjects with one or more treatment-emergent adverse events

- The proportion of patients with one or more treatment-emergent serious adverse events

- Tertiary/Exploratory Endpoints:

- Pattern of change over time at baseline (prior to the start of daratumumab treatment), 12 weeks (midpoint), 25 weeks (endpoint), and 36 weeks (12 weeks after completion of treatment) in the following cognitive outcome measures: ADAS-cog/11, ADAS-cog/12, MMSE, CDR-SB, ADCOMS

- Change from baseline at 25 weeks in CD38 expression on circulating (whole blood) CD8+ T-cells measured with flow cytometry

- Change from baseline at 25 weeks in metabolite ratios: N-acetylaspartate/creatine (NAA/Cr), myo-inositol/creatine (mI/Cr), choline/creatine (Cho/Cr), and N-acetylaspartate/myo-inositol (NAA/mI) on single-voxel protein magnetic resonance spectroscopy from the precuneus and posterior cingulate region

9.2 SAMPLE SIZE DETERMINATION

This is a pilot study, the purpose of which is explore whether there is a clinically meaningful efficacy signal for daratumumab in patients with mild to moderate Alzheimer's disease. The proposed sample size of 15 patients is based on feasibility and availability of resources, and not on a formal power calculation.

The following table provides estimates of proportions and their associated 95% confidence intervals for a sample size of 15 subjects.

N=15			
Observed Number Responding	**Observed Proportion Responding**	**Exact Lower 95% Confidence Interval**	**Exact Upper 95% Confidence Interval**
0	0.000	0.000	0.218
1	0.067	0.002	0.319
2	0.133	0.017	0.405
3	0.200	0.043	0.481
4	0.267	0.078	0.551
5	0.333	0.118	0.616
6	0.400	0.163	0.677
7	0.467	0.213	0.734
8	0.533	0.266	0.787
9	0.600	0.323	0.837
10	0.667	0.384	0.882
11	0.733	0.449	0.922
12	0.800	0.519	0.957
13	0.867	0.595	0.983
14	0.933	0.681	0.998
15	1.000	0.782	1.000

For a sample size of 15 subjects, if 7 patients respond, the lower limit of the exact 95% binomial confidence interval is 0.213, (i.e., we are 95% certain that the true proportion with a response is no lower than 0.213). Based on previous results in patients with mild to moderate AD maintained on stable treatment with a cholinesterase inhibitor, the expected responder rate at 25 weeks (defined as improvement in ADAS-cog/11 score of ≥ 4 points) is 20% (0.20) (Rockwood et al. 2007). Therefore, if 7 or more of 15 subjects respond, we would consider further study of daratumumab warranted.

9.3 POPULATIONS FOR ANALYSES

Data from all subjects who receive at least one dose of study medication will be included in all efficacy and safety analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics (mean and standard deviation, median, minimum, and maximum) for all outcome measures at each timepoint will be calculated.

Plots of the data, (including spaghetti plots) will be used to visualize patterns in the data. Additional post hoc exploratory analyses may be carried out.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The 11-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog/11) has been a standard cognitive outcome measure in clinical trials for patients with mild to moderate AD. Total scores range from 0–70, with higher scores indicating greater cognitive impairment. The average expected worsening (increase) on this scale over 6 months in this population is in the range of 2 to 3 points. A clinically meaningful improvement (decrease) on this scale has been deemed to be 4 or more points. Based on previous results in patients with mild to moderate AD maintained on stable treatment with a cholinesterase inhibitor, the expected responder rate at 25 weeks (defined as improvement in ADAS-cog/11 score of ≥ 4 points) is 20% (0.20) (Rockwood et al. 2007).

A patient will be considered a responder if they improve by a minimum of 4 points on the ADAS-cog/11 scale at 25 weeks compared to baseline. The proportion of patients who respond to daratumumab will be estimated, and the associated 95% exact binomial confidence interval will be calculated.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary Efficacy Endpoints will consist of the proportion of subjects who are unchanged or improved from baseline to 25 weeks on ADAS-cog/12 score (standard 11 items plus delayed word recall), Mini Mental State Examination (MMSE) score, Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score, and AD Composite Score (ADCOMS).

All analyses will be carried out separately for each secondary endpoint listed above.

For each measure of cognitive response, a patient will be classified as stable or improved if the score at 25 weeks is the same or better than at baseline. The proportion of patients who are stable/improved, and the associated 95% exact binomial confidence interval will be calculated.

9.4.4 SAFETY ANALYSES

The proportion of patients with one or more treatment-emergent adverse events will be estimated, and the associated 95% exact binomial confidence interval will be calculated.

The proportion of patients with one or more treatment-emergent serious adverse events will be estimated, and the associated 95% exact binomial confidence interval will be calculated.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics (mean and standard deviation, median, minimum, and maximum for continuous factors; frequency and proportion for categorical factors) for demographic and clinical factors (including age, sex, years of education, and baseline MMSE score) will be calculated.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 TERTIARY/EXPLORATORY ANALYSES

The pattern of cognitive response to daratumumab, as measured by ADAS-cog/11, ADAS-cog/12, MMSE, CDR-SB, and ADCOMS, will be examined over time at baseline (prior to the start of daratumumab treatment), 12 weeks (midpoint), 25 weeks (endpoint), and 36 weeks (12 weeks after completion of treatment).

For each measure of cognitive response, repeated measures analysis of variance (RMANOVA) where time (baseline, 12 weeks, 25 weeks, 36 weeks) is the within subjects effect, and there is not between subjects effect, will be used to examine the changes in each outcome over time.

CD38 expression in circulating CD8+ T-cells will be measured with flow cytometry at baseline and at 25 weeks. The paired t-test will be used to examine whether there is a change at 25 weeks vs baseline.

Cerebral metabolite ratios will be measured on single-voxel protein magnetic resonance spectroscopy from the precuneus and posterior cingulate region at baseline and at 25 weeks, including:

- N-acetylaspartate/creatine (NAA/Cr)
- myo-inositol/creatine (mI/Cr)
- choline/creatine (Cho/mI)
- N-acetylaspartate/myo-inositol (NAA/mI)

All analyses will be carried out separately for each metabolite ratio endpoint listed above. The paired t-test will be used to examine whether there is a change at 25 weeks vs baseline for each factor listed above.

If the usual assumptions of the proposed parametric models are not met, an appropriate transformation or a suitable non-parametric method will be used.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the the subject, their study partner, and the subject's legally authorized representative (if applicable), and written documentation of informed consent is required prior to starting any study-related procedure.

The following consent materials are submitted with this protocol:

- Subject Informed Consent Form
- Study Partner Information and Consent Form

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual’s agreeing to participate in the study and continues throughout the individual’s study participation. Potential participants will be provided with a copy of the informed consent document ahead of research participation. This will allow the subject and their legally authorized representative (if applicable) the necessary time to carefully review detailed information about the study procedures, risks, and benefits, and ask questions or express concerns prior to making a decision about whether to participate. Prior to the initiation of any screening or study-specific procedures, the investigator or his representative will explain the nature of the study to the subject, their study partner, and the subject's legally authorized representative (if applicable), and answer all questions regarding this study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Due to the inherent nature of the study population, with cognitive impairment due to Alzheimer’s disease, it is anticipated that many of these subjects will lack decisional capacity to provide informed consent. Accordingly, all potential subjects will be assessed for capacity to provide informed consent by one of the study physicians, who are either neurologists or geriatric psychiatrists with extensive experience in

assessing decisional capacity. If a subject is determined to lack capacity to provide informed consent, surrogate consent will need to be obtained from a legally authorized representative. In that instance, the subject will also need to provide written assent to participate in the study. Each informed consent will be reviewed, signed and dated by the subject or their legally authorized representative (if applicable), the person who administered the informed consent, and any other signatories according to local requirements. A separate informed consent will also be reviewed, signed, and dated by the subject's study partner prior to beginning any study related screening activities. A copy of each informed consent will be given to the subject and their study partner and each original will be placed in the subject's study chart. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject and study partner received signed copies.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Janssen Scientific Affairs, LLC, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy Janssen Scientific Affairs, LLC, the IRB, and/or the Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the investigator, research staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of subject or their legally authorized representative.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Institution, representatives of the Institutional Review Board (IRB), regulatory agencies, or the pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or regulatory requirements.

The study data entry and study management systems used by clinical site research staff will be secured and password protected. The Feinstein Institute for Medical Research will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biostatistics Unit of the Feinstein Institute for Medical Research. The interactive development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at the Feinstein and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended to Northwell Health's researchers by our Clinical Research Service, Research Compliance Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports more than 2500 active institutional partners and other institutions in more than 100 countries (www.projectredcap.org). De-identified research data may be stored on portable electronic devices (e.g. laptops, tablets, flash drives, etc.). All such devices will be encrypted as per Northwell Health policy (*www.projectredcap.org*).

Certificate of Confidentiality:

To further protect the privacy of study participants, a Certificate of Confidentiality (CoC) will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Feinstein Institute for Medical Research.

When the study is completed, access to study data will be provided through the Feinstein Institute for Medical Research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Clinical Monitor**	**Independent Safety Monitor**
Marc L. Gordon, MD	Office of Research Compliance	Monique A. Hartley-Brown, MD
Feinstein Institute for Medical Research	Northwell Health	Monter Cancer Center
350 Community Drive, 4th floor Manhasset, NY 11030	1111 Marcus Avenue Lake Success, NY 11042	450 Lakeville Road Lake Success, NY 11042
(516) 562-3492	(516) 266-5024	(516) 734-3532
MLGordon@northwell.edu	ORC@northwell.edu	MHartleyBr@northwell.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an Independent Safety Monitor (ISM), a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by review of adverse events, immediately after they occur or are reported, with follow-up through resolution. The ISM will be notified of SAEs by the study team within 24 hours of knowledge of the event. The ISM will be notified of unexpected problems as soon as possible, but within 5 business days of knowledge of the event. The ISM will be notified within 15 business days of severe (NCI CTCAE Grade 3 or 4) nonserious AEs. The study team will report aggregate mild to moderate (NCI CTCAE Grade 1 or 2) nonserious AEs to the ISM at 4-month intervals. The ISM evaluates individual and cumulative participant data when making recommendations regarding the safe continuation of the study. The ISM will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Clinical Monitor, or designee, will perform the following oversight and monitoring tasks in accordance with protocol specific requirements, Good Clinical Practice Guidelines, and Northwell Health Policy GR080, “Human Subject Research Oversight and Monitoring”.

These tasks will include, but are not limited to:

1. Quarterly review of essential required documents in the Investigator site file. The first review will be completed prior to study initiation. All reviews will include:
   - Study form 1572
   - All study staff CVs and any relevant medical licenses
   - Staff training documentation
   - Site delegation of responsibility log
   - Subject enrollment log
   - IRB communications and approvals
   - Current and prior protocol versions
   - Current and prior consent forms
   - Laboratory certifications and reference ranges

2. Review of the informed consent process and documentation for each subject (100%) who consents to participate in the study within 5 business days of consent.

3. Review of subject source documentation with inclusion/exclusion criteria (100%).

4. Review of all visit specific case report forms (100%) and partial congruence check with electronic data entry on a monthly basis (two randomly selected documents per participant visit).

5. Review of all minor protocol deviations and documentation on a monthly basis (100%).

6. Review and reporting of all (100%) internal serious adverse events or major protocol deviations within 5 business days of occurrence

Any issues identified will be immediately communicated to the Principal Investigator for corrective action.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the study staff for clarification/resolution.

Quality assurance (QA) will be assessed and documented through the clinical monitoring plan detailed in Section 10.1.7 above. In addition, quality will be ensured by adherence to and monitoring of the following:

1. Biological specimens collected for this protocol will be handled and processed according to Northwell Health Laboratory Science Specimen Collection and Handling Guidelines. Monitoring of clinical case report forms will include analysis of compliance with specimen collection and

consistency of the quality of results. All calibration and quality assurance of laboratory testing equipment is routinely performed by the Northwell Core Laboratory.

2. All medical equipment used in the care of research subjects, including but not limited to, blood pressure cuff, thermometer, electrocardiogram, pulse oximeter, etc. are routinely checked by Northwell Health's bioengineering group and labeled with safety stickers at 6-month intervals.

3. Disposable patient supplies; blood collection tubes, phlebotomy supplies, syringes, etc. are routinely checked for expiration dates on a monthly basis.

4. Custom training plans will be created for nurses that will administer study medication. Documentation of successful completion of training will be required before study nurses will be authorized to administer study medication.

5. Investigational pharmacy records will be reviewed biannually, or more often as needed, to include receipt of investigational drug, storage records, temperature logs, and dispensing logs.

The Clinical Monitor will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements [e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)].

The investigational site will provide direct access to all source data/documents, and reports for the purposes of monitoring and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture

system provided by the Feinstein Institute for Medical Research. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 7 years after study close-out, a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention, whichever is longer. No records will be destroyed without the written consent of Janssen Scientific Affairs, LLC.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report protocol deviations. Major protocol deviations (those that affect subject safety, rights, welfare or data integrity) must be reported to the IRB within ten (10) working days of discovery. Minor protocol deviations (those that do not affect subject safety, rights, welfare or data integrity) may be reported to the IRB at continuing review, using a protocol deviation log. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in a peer-reviewed journal. Manuscripts and presentations will be reviewed by Janssen Scientific Affairs, LLC prior to submission to any journal or conference.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with Northwell Health has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-cognitive subscale
ADCOMS	AD Composite Score
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
CBC	Complete Blood Count
CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CFR	Code of Federal Regulations
Cho	Choline
CMP	Comprehensive Metabolic Panel
CoC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
Cr	Creatine
CSM	Clinical Supplies Management Holdings, Inc.
CTCAE	Common Terminology Criteria for Adverse Events
DARA-SC	Daratumumab Subcutaneous
DP	Drug Product
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCP	Health Care Provider
HCV	Hepatitis C Virus
HCVAb	Hepatitis C Virus Antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HIVAg/Ab	Human Immunodeficiency Virus Antigen/Antibody
^{1}H-MRS	Proton Magnetic Resonance Spectroscopy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG1κ	Immunoglobulin G1 Kappa
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction

ISM	Independent Safety Monitor
IV	Intravenous
mAb	Monoclonal Antibody
MHIS	Modified Hachinski Ischemia Score
mI	Myo-Inositol
mL	Milliliter
MMSE	Mini-Mental State Examination
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NAA	N-Acetylaspartate
NaCl	Sodium Chloride
NCI	National Cancer Institute
NIA-AA	National Institute on Aging-Alzheimer's Association
OHRP	Office for Human Research Protections
ORR	Overall Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PQC	Product Quality Complaint
PT	Prothrombin Time
QA	Quality Assurance
QC	Quality Control
REDCap	Research Electronic Data Capture
rHuPH20	Recombinant human hyaluronidase
RMANOVA	Repeated Measures Analysis of Variance
RT	Room Temperature
SAE	Serious Adverse Event
SC	Subcutaneous
SoA	Schedule of Activities
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
TSH	Thyroid-Stimulating Hormone
UP	Unanticipated Problem
US	United States
VGPS	Very Good Partial Response

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

Askoy P, et al. Regulation of SIRT 1 mediated NAD dependent deacetylation: a novel role for the multifunctional enzyme CD38. Biochem Biophys Res Commun. 2006 Oct 13;349(1):353-9. PMID: 16935261 DOI: 10.1016/j.bbrc.2006.08.066

Blacher E, et al. Alzheimer's disease pathology is attenuated in a CD38-deficient mouse model. Ann Neurol. 2015 Jul;78(1):88-103. PMID: 25893674 DOI: 10.1002/ana.24425

Camacho-Pereira J, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. Cell Metab. 2016 Jun 14;23(6):1127-1139. PMID: 27304511 DOI: 10.1016/j.cmet.2016.05.006

Chari A, et al. Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma: part 2 safety and efficacy update of the open-label, multicenter, phase 1b study (PAVO) [abstract]. *Blood*. 2018;132(suppl 1):Abstract 1995.

Folstein MF, et al. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98. PMID: 1202204

Heneka MT, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015 Apr;14(4):388-405. PMID: 25792098 DOI: 10.1016/S1474-4422(15)70016-5

Hughes CP, et al. A new clinical scale for the staging of dementia. Br J Psychiatry. 1982 Jun;140:566-72. PMID: 7104545

Imai S, Guarante L. NAD+ and sirtuins in aging and disease. Trends Cell Biol. 2014 Aug;24(8):464-71. PMID: 24786309 DOI: 10.1016/j.tcb.2014.04.002

Krejcik J, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood. 2016 Jul 21;128(3):384-94. PMID: 27222480 DOI: 10.1182/blood-2015-12-687749

Lynch CA, et al. The Clinical Dementia Rating Sum of Box score in mild dementia. Dement Geriatr Cogn Disord. 2006;21(1):40–43. PMID: 16254429 DOI: 10.1159/000089218

Mayo L, et al. Dual role of CD38 in microglial activation and activation-induced cell death. J Immunol. 2008 Jul 1;181(1):92-103. PMID: 18566373 DOI:https://doi.org/10.4049/jimmunol.181.1.92

McKhann GM, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimers Dement. 2011 May;7(3):263-9. PMID: 21514250 DOI: 10.1016/j.jalz.2011.03.005.

Perez Ortiz JM, Swerdlow RH. Mitochondrial dysfunction in Alzheimer's disease: Role in pathogenesis and novel therapeutic opportunities. Br J Pharmacol. 2019 Jan 24. [Epub ahead of print] PMID: 30675901 DOI:10.1111/bph.14585

Raina P, et al. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med. 2008 Mar 4;148(5):379-97. PMID: 18316756

Rockwood K, et al. The clinical meaningfulness of ADAS-Cog changes in Alzheimer's disease patients treated with donepezil in an open-label trial. BMC Neurol. 2007 Aug 30;7:26. PMID: 17760991 DOI: 10.1186/1471-2377-7-26

Rosen WG, et al. Pathological verification of ischemic score in differentiation of dementias. Ann Neurol. 1980 May;7(5):486-8. PMID: 7396427 DOI: 10.1002/ana.410070516

Rosen WG, et al. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984 Nov;141(11):1356-64. PMID: 6496779 DOI: 10.1176/ajp.141.11.1356

Sano M, et al. Adding delayed recall to the Alzheimer Disease Assessment Scale is useful in studies of mild cognitive impairment but not Alzheimer disease. Alzheimer Dis Assoc Disord. 2011 Apr-Jun;25(2):122-7. DOI: 10.1097/WAD.0b013e3181f883b7

Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol. 1986 June;5(1/2):165-173.

Usmani SZ, et al. Open-label, multicenter, dose escalation Phase 1b study to assess the subcutaneous delivery of daratumumab in patients (pts) with relapsed or refractory multiple myeloma (PAVO). Blood. 2016 128:1149

Vercruyssen M, et al. The daratumumab crosses the blood brain barrier. Clinical Lymphoma, Myeloma and Leukemia. 2018;18:S289

Verdin E. NAD^+ in aging, metabolism, and neurodegeneration. Science. 2015 Dec 4;350(6265):1208-13. PMID: 26785480 DOI: 10.1126/science.aac4854

Wang J, et al. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. J Neurol Neurosurg Psychiatry 2016;87:993-999. PMID: 27010616 PMCID: PMC5013117 DOI: 10.1136/jnnp-2015-312383

Zhang R, et al. Systemic immune system alterations in early stages of Alzheimer's disease. J Neuroimmunol. 2013 Mar 15;256(1-2):38-42. PMID: 23380586 DOI: 10.1016/j.jneuroim.2013.01.002