A Study of Daratumumab With the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Participants With Relapsed or Refractory Multiple Myeloma

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT02519452	RECRUITING	AUGUST 11, 2015	JANUARY 3, 2020

STUDY DESCRIPTION

Brief Summary

The purpose of the study is to evaluate the pharmacokinetics and safety from the mixture of daratumumab and rHuPH20 prepared immediately before administration via Subcutaneous (SC) delivery (Part 1) and CF (co-formulated daratumumab and rHuPH20 preparation) administration via SC delivery of daratumumab (Part 2) and to evaluate the safety of Dara-CF 1800 milligram (mg) SC delivery without pre-dose and post-dose corticosteroids (Part 3).

Condition or Disease: Multiple Myeloma

Intervention/treatment: Drug: Daratumumab Subcutaneous (SC) Administration
Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration

Phase: Phase 1

DETAILED DESCRIPTION

This is an open-label (identity of assigned study drug will be known), multicenter, 3-part, Phase 1b dose escalation/expansion study to evaluate the safety, pharmacokinetics (study of what the body does to a drug), and antitumor activity of SC delivery of daratumumab to participant with relapsed or refractory multiple myeloma. Up to approximately 53 participants in part 1, 80 participants in part 2 and 15 participants per corticosteroid tapering cohort (up to approximately 30 participants total) in Part 3 will be enrolled. The purpose of Part 1 is to select an appropriate SC therapeutic dose for the mixture of daratumumab with rHuPH20 based on safety and pharmacokinetics. This dose, selected from part 1 will be the initial dose for the co-formulated daratumumab and rHuPH20 preparation to be evaluated in Part 2. The purpose of Part 2 is to evaluate the SC delivery of CF and confirm the dose level selected from Part 1 based on the pharmacokinetics, safety, and antitumor activity. The purpose of Part 3 is to evaluate the safety of Dara-CF 1800 mg SC delivery without pre-dose and post-dose corticosteroids. Participant's safety will be monitored throughout the study.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 108 participants

Intervention Model : Parallel Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab With the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Subjects With Relapsed or Refractory Multiple Myeloma

Actual Study Start Date: October 2015

Estimated Primary Completion Date: December 2017

Actual Study Completion Date: November 2022

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Part 1: Cohort 1 Participants will receive 1200 mg (daratumumab 1200 milligram (mg) with Recombinant Human Hyaluronidase [rHuPH20] 30,000 U) via mixing immediately before Subcutaneous (SC) infusion once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and then every 4 weeks in subsequent cycles until disease progression.	Drug: Daratumumab Subcutaneous (SC) Administration Participants will receive Daratumumab mixed with rHuPH20 in part 1 and co-formulated with rHuPH20 in part 2 and part 3 administered via SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles. Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration Participants will receive Recombinant Human Hyaluronidase [rHuPH20]) mixed with Daratumumab in part 1 and co-formulated with Daratumumab in part 2 and part 3 administered as SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles.

Experimental: Part 1: Cohort 2 Participants will receive 1800 mg (daratumumab 1800 milligram (mg) with Recombinant Human Hyaluronidase [rHuPH20] 45,000 U) via mixing immediately before SC infusion once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and then every 4 weeks in subsequent cycles until disease progression.	Drug: Daratumumab Subcutaneous (SC) Administration Participants will receive Daratumumab mixed with rHuPH20 in part 1 and co-formulated with rHuPH20 in part 2 and part 3 administered via SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles. Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration Participants will receive Recombinant Human Hyaluronidase [rHuPH20]) mixed with Daratumumab in part 1 and co-formulated with Daratumumab in part 2 and part 3 administered as SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles.
Experimental: Part 1: Cohort 3 Participants will receive mixture of daratumumab and rHuPH20 prepared immediately before administration via Subcutaneous (SC) delivery at a dose which will be decided by Study Evaluation Team (SET) once weekly by SC infusion in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and then every 4 weeks in subsequent cycles until disease progression. Also up to three additional optional cohorts (Cohorts 3b, 3c, and 3d) may be enrolled to repeat a dose level of daratumumab.	Drug: Daratumumab Subcutaneous (SC) Administration Participants will receive Daratumumab mixed with rHuPH20 in part 1 and co-formulated with rHuPH20 in part 2 and part 3 administered via SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles. Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration Participants will receive Recombinant Human Hyaluronidase [rHuPH20]) mixed with Daratumumab in part 1 and co-formulated with Daratumumab in part 2 and part 3 administered as SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles.
Experimental: Part 2: Cohort 4 Participants will receive 1800 mg co-formulated daratumumab and rHuPH20 preparation initially administered by SC injection once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and then every 4 weeks in subsequent cycles. The dose level and schedule for any additional cohorts would be selected based on the daratumumab pharmacokinetic profile and safety profile (reviewed by the SET) that will be observed in Cohort 4.	Drug: Daratumumab Subcutaneous (SC) Administration Participants will receive Daratumumab mixed with rHuPH20 in part 1 and co-formulated with rHuPH20 in part 2 and part 3 administered via SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles. Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration Participants will receive Recombinant Human Hyaluronidase [rHuPH20]) mixed with Daratumumab in part 1 and co-formulated with Daratumumab in part 2 and part 3 administered as SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles.
Experimental: Part 3: Dara-CF 1800 mg Participants will receive co-formulated daratumumab 1800 mg and rHuPH20 preparation (Dara-CF) initially administered by SC injection once weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and then every 4 weeks in subsequent cycles.	Drug: Daratumumab Subcutaneous (SC) Administration Participants will receive Daratumumab mixed with rHuPH20 in part 1 and co-formulated with rHuPH20 in part 2 and part 3 administered via SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles. Drug: Recombinant Human Hyaluronidase [rHuPH20]) SC Administration Participants will receive Recombinant Human Hyaluronidase [rHuPH20]) mixed with Daratumumab in part 1 and co-formulated with Daratumumab in part 2 and part 3 administered as SC administration once weekly in Cycles 1 (each cycle is 28 days) and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in subsequent cycles.

OUTCOME MEASURES

Primary Outcome Measures:
1. Serum Trough Concentrations (Ctrough) of Daratumumab [Time Frame: Up to cycle 3 (each cycle 28 days) Day 1]
Ctrough: the concentration prior to study drug administration.
2. Part 1, 2 and 3: Number of Participants with Adverse Events (AEs) and Serious AEs [Time Frame: Screening up to follow-up (30 days after last dose administration) (Approximately up to 3.4 years)]
An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

Secondary Outcome Measures:
1. Part 1, 2 and 3: Serum Concentration of Daratumumab and Recombinant Human Hyaluronidase (rHuPH20) (Plasma) Antibodies [Time Frame: Approximately 2 years]
Serum levels of antibodies to Daratumumab and rHuPH20 for evaluation of potential immunogenicity.
2. Part 1, 2 and 3: Percentage of Participants with Complete Response (CR) [Time Frame: Approximately 2 years]
CR is Defined as the proportion of Participants achieving CR (including sCR) according to the International Myeloma Working Group (IMWG) criteria.
3. Part 1, 2 and 3: Percentage of Participants With Overall Response Rate (ORR) [Time Frame: Approximately 2 years]
Overall response rate is defined as the percentage of participants who achieve complete response, stringent complete response (sCR), partial response or very good partial response (VGPR) according to the International Myeloma Working Group criteria, during or after study treatment.
4. Part 1, 2 and 3: Duration of Response (DR) [Time Frame: Approximately 2 years]
The DR is time from date of initial documentation of response (PR or better) to date of first documented PD, as defined by IMWG criteria.
5. Part 1, 2 and 3: Time to Response [Time Frame: Approximately 2 years]
Time to response is defined as the time from the date of first dose of study treatment to the date of the first documentation of observed response (CR or PR or better than PR)

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
- Participants proven to have multiple myeloma (MM) diagnosis according to the International Myeloma Working Group (IMWG) diagnostic criteria
- Measurable disease as defined by any of the following: (a) immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [M-protein] level >=1.0 gram/deciliter [g/dL] or urine M-protein level greater than or equal to (>=) 200 milligram[mg]/24 hours[hrs]; or (b) IgA, IgD, or IgE multiple myeloma (serum M-protein level >= 0.5 g/dL or urine M-protein level >= 200 mg/24 hrs); or (c) light chain multiple myeloma (serum immunoglobulin free light chain >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio)
- Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
- Pretreatment clinical laboratory values must meet protocol-defined parameters during the Screening phase
- Man, who is sexually active with a woman of child-bearing potential and has not had a vasectomy, must agree to use a barrier method of birth control example (eg), either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 3 months after receiving the final dose of study drug
- Relapsed or refractory disease. Relapse is defined as progression of disease after an initial response to previous treatment, more than 60 days after cessation of treatment. Refractory disease is defined as less than (=) 2 treatment lines of anti-myeloma therapy. Prior lines of therapy must include a proteasome inhibitor (PI) (eg, bortezomib, carfilzomib) and an immunomodulatory drug (IMiD) (example, thalidomide, lenalidomide, pomalidomide) in any order during the course of treatment. Each prior line of therapy may consist of one or more agents and may include induction, hematopoietic stem cell transplantation, and/or maintenance therapy. Radiotherapy, bisphosphonates, or a single short course of steroids is not considered a prior line of therapy

Exclusion Criteria:
- Participant has received daratumumab or other anti-cluster of differentiation 38 (anti-CD38) therapies previously
- Participant has received anti-myeloma treatment within 2 weeks before Cycle 1 Day 1
- Participant has previously received an allogenic stem cell transplant; or participant has received autologous stem cell transplantation (ASCT) within 12 weeks before Cycle 1 Day 1
- Participant has a history of malignancy (other than multiple myeloma) within 5 years before Cycle 1 Day 1 (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence)
- Participant is exhibiting clinical signs of meningeal involvement of multiple myeloma

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CONTACTS AND LOCATIONS

Contacts

Contact:

Locations

United States, Georgia	Winship Cancer Institute Emory University	Atlanta
United States, New York	Mt. Sinai School of Medicine	New York
United States, North Carolina	Levine Cancer Institute	Charlotte
United States, Pennsylvania	University of Pennsylvania-Abramson Cancer Center	Philadelphia
Denmark	Vejle Sygehus	Vejle
France	Hôpital Huriez, CHRU Lille	Lille
France	CHU de Nantes hôtel-Dieu	Nantes Cedex 1
France	Centre hospitalier Lyon-Sud	Pierre-Bénite
France	CHU Bretonneau	Tours cedex
Netherlands	VU Medisch Centrum	Amsterdam
Netherlands	Erasmus MC	Rotterdam
Spain	Hosp. Univ. Germans Trias I Pujol	Badalona
Spain	Clinica Univ. de Navarra	Pamplona
Spain	Hosp. Clinico Univ. de Salamanca	Salamanca
Sweden	Haematology Centre, R 51	Stockholm

Sponsors and Collaborators

Janssen Research & Development, LLC

Investigator

Study Director :	Janssen Research & Development, LLC Clinical Trial	Janssen Research & Development, LLC

MORE INFORMATION

Responsible Party :	Janssen Research & Development, LLC
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