8013

Subcutaneous Daratumumab (DARA) in Patients (Pts) With Relapsed or Refractory Multiple Myeloma (RRMM): Part 2 Update of the Open-label, Multicenter, Dose-escalation Phase 1b Study (PAVO)

Ajai Chari,[1,*] Saad Z. Usmani,[2] Maria-Victoria Mateos,[3] Niels WCJ van de Donk,[4] Jonathan L. Kaufman,[5] Philippe Moreau,[6] Albert Oriol,[7] Torben Plesner,[8] Lotfi Benboubker,[9] Kevin Liu,[10] Peter Hellemans,[11] Tara Masterson,[12] Pamela L. Clemens,[12] Andrew Farnsworth,[13] Hareth Nahi,[14] Jesus San-Miguel[15]

[1]Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY, USA; [2]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [3]University Hospital of Salamanca/IBSAL, Salamanca, Spain; [4]Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; [5]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [6]University Hospital of Nantes, Nantes, France; [7]Institut Català d'Oncologia, HGTiP, Barcelona, Spain; [8]Vejle Hospital and University of Southern Denmark, Vejle, Denmark; [9]Service d'Hématologie et Thérapie Cellulaire, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire (CHRU), Tours, France; [10]Janssen Research & Development, LLC, Raritan, NJ, USA; [11]Janssen Research & Development, Beerse, Belgium; [12]Janssen Research & Development, LLC, Spring House, PA, USA; [13]Janssen Research & Development, LLC, High Wycombe, United Kingdom; [14]Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; [15]Clínica Universidad de Navarra-CIMA, IDISNA, CIBERONC, Pamplona, Spain.

Email: ajai.chari@mountsinai.org

*Presenting author.

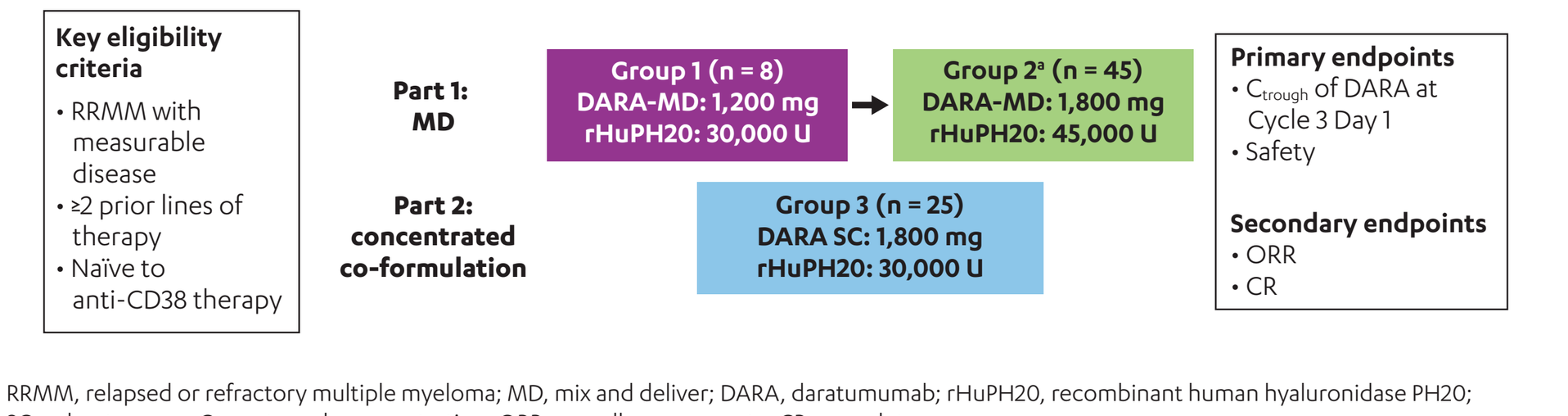
INTRODUCTION

- Daratumumab is a human, CD38-targeted monoclonal antibody with a direct on-tumor and immunomodulatory mechanism of action
  - The direct on-tumor actions of daratumumab are mediated by complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and apoptosis[1-4]
  - The immunomodulatory actions of daratumumab lead to modulation of the tumor microenvironment, clonal expansion of cytotoxic T cells, an increase in helper T cells, a depletion of $CD38^+$ immunosuppressive cells, and an increase in $CD38^+$ granzyme B^+ cells[5-7]
- Intravenous (IV) daratumumab 16 mg/kg is approved as a monotherapy and in combination with bortezomib/dexamethasone, lenalidomide/dexamethasone, or pomalidomide/dexamethasone (United States only) in patients with relapsed or refractory multiple myeloma (RRMM)[8,9]
  - In clinical studies, the median durations of the first, second, and subsequent daratumumab IV infusions were 7.0, 4.3, and 3.4 hours, respectively[8]
  - Infusion-related reactions (IRRs) are manageable and occur primarily during the first infusion[10-12]
  - The maximum daratumumab C_{trough} (trough concentration at the end of weekly dosing, which is on Cycle 3 Day 1 in monotherapy) has been shown in population pharmacokinetic and exposure-response analyses to be related to overall response rate in multiple myeloma[13]
- Recently, IV daratumumab 16 mg/kg in combination with bortezomib, melphalan, and prednisone was approved for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant[8]
- To facilitate subcutaneous (SC) delivery, recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.) temporarily breaks down the hyaluronan barrier, allowing rapid administration of larger volumes of injected drugs[14]
- A mix-and-deliver formulation of daratumumab and rHuPH20 (DARA-MD; given SC by means of a syringe pump) was well tolerated, with low rates of IRRs and similar efficacy to IV daratumumab[15]
  - Deep responses, including a stringent complete response, were observed
- A pre-mixed co-formulation of daratumumab and rHuPH20 (DARA SC) with a higher daratumumab concentration, lower injection volume, and shorter injection time was developed, enabling manual SC injection in the abdomen[16]
- We present updated safety, pharmacokinetic, and efficacy findings of DARA SC in patients with RRMM (Part 2 of PAVO)

METHODS

Study Design, Eligibility Criteria, and Treatment

- PAVO is a phase 1b, open-label, multicenter, dose-finding, proof-of-concept study in patients with RRMM (**Figure 1**)
- RRMM patients had received ≥2 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug
- In Part 1 of the study, DARA-MD was administered by SC infusion over 20 to 30 minutes through a syringe pump to determine the recommended dose for Part 2
  - Patients received 28-day cycles of daratumumab 1,200 mg + rHuPH20 30,000 U (in 60 mL; Group 1) or daratumumab 1,800 mg + rHuPH20 45,000 U (in 90 mL; Group 2) following the approved IV monotherapy dosing schedule (weekly [QW] in Cycles 1 and 2, every 2 weeks [Q2W] in Cycles 3 through 6, and every 4 weeks [Q4W] thereafter)[8]
- In Part 2 of the study, a concentrated co-formulation of the selected daratumumab (1,800 mg) and rHuPH20 (30,000 U; in 15 mL) dose in a single, pre-mixed vial was administered over 3 to 5 minutes by manual SC injection (DARA SC)
- Pre- and/or post-infusion medications included acetaminophen, diphenhydramine, montelukast, and methylprednisolone



Key eligibility criteria
• RRMM with measurable disease
• ≥2 prior lines of therapy
• Naïve to anti-CD38 therapy
Part 1: MD
Group 1 (n = 8) DARA-MD: 1,200 mg rHuPH20: 30,000 U
Group 2[a] (n = 45) DARA-MD: 1,800 mg rHuPH20: 45,000 U
Part 2: concentrated co-formulation
Group 3 (n = 25) DARA SC: 1,800 mg rHuPH20: 30,000 U
Primary endpoints
• Ctrough of DARA at Cycle 3 Day 1
• Safety
Secondary endpoints
• ORR
• CR

RRMM, relapsed or refractory multiple myeloma; MD, mix and deliver; DARA, daratumumab; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response.
[a]C_{trough} on Cycle 3 Day 1 in Group 1 supported dose selection for Group 2. The study evaluation team reviewed safety after Cycle 1 and pharmacokinetics after Cycle 3 Day 1 for each group.

Figure 1. PAVO study design.

RESULTS

Patients and Treatments

- At the December 13, 2017 clinical cutoff, 25 patients were enrolled in Part 2 (DARA SC 1,800 mg; **Table 1**)
- For Part 2, the median (range) duration of follow-up was 6.5 (2.4-7.2) months

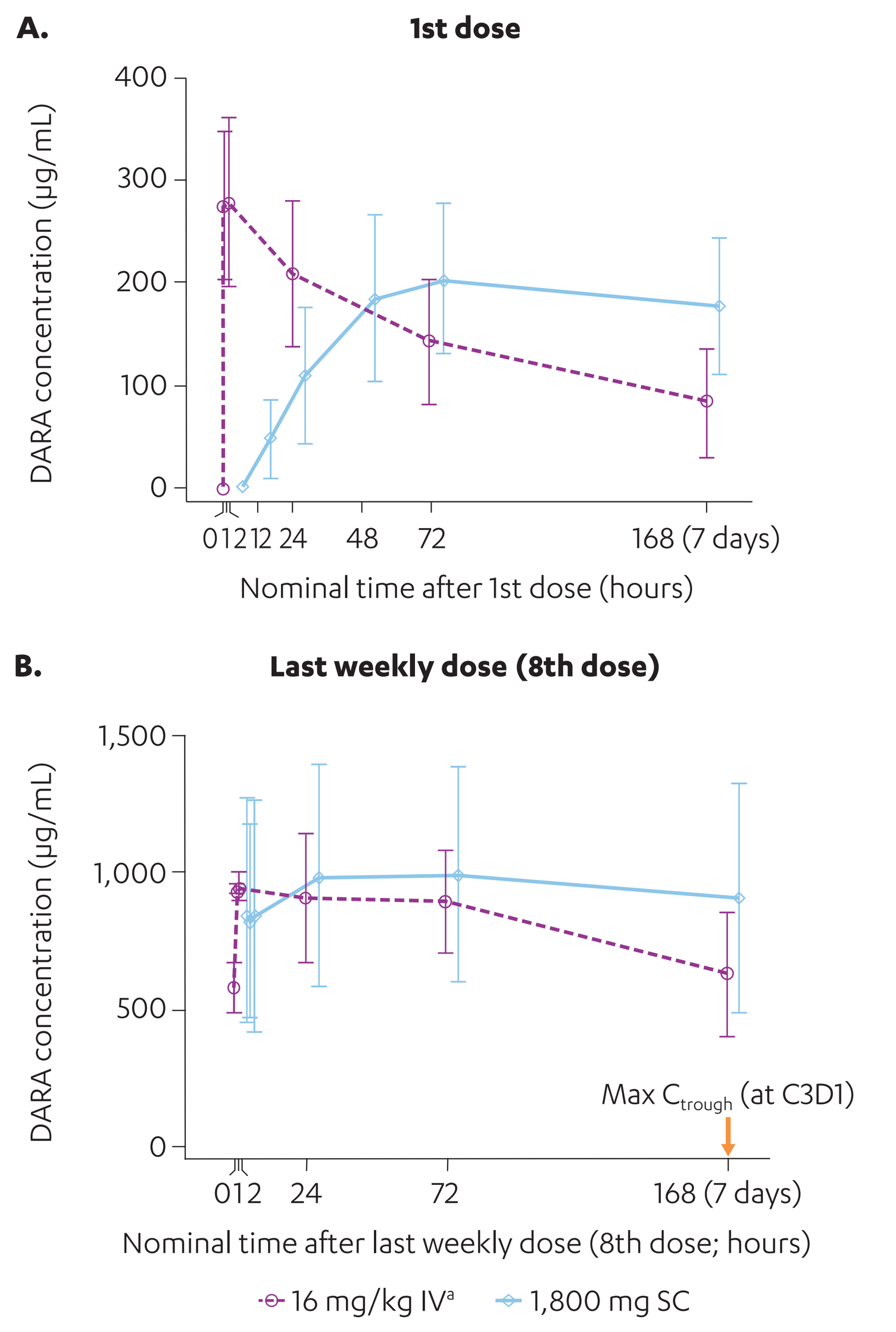
Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	DARA SC 1,800 mg (n = 25)
Age, y	
Median (range)	68 (51-85)
≥75, n (%)	6 (24)
Median (range) weight, kg	70.9 (52.0-104.8)
Baseline ECOG status, n (%)	
0	11 (44)
1	13 (52)
2	1 (4)
ISS stage, n[a]	24
I, n (%)	13 (54)
II, n (%)	5 (21)
III, n (%)	6 (25)
Median (range) time from diagnosis, y	5.9 (2.1-12.8)
Type of myeloma, n	24
IgG, n (%)	13 (54)
Cytogenetic risk, n[b]	16
Standard risk	12 (75)
High risk	4 (25)[c]
Prior lines of therapy, n (%)	
Median (range)	3 (2-9)
≤3	17 (68)
>3	8 (32)
Prior ASCT, n (%)	17 (68)
Prior PI, n (%)	25 (100)
Bortezomib	24 (96)
Prior IMiD, n (%)	25 (100)
Lenalidomide	23 (92)
Refractory to, n (%)	
Bortezomib	16 (64)
Lenalidomide	14 (56)
Both PI and IMiD	14 (56)
Last line of therapy	19 (76)

DARA, daratumumab; SC, subcutaneous; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug; FISH, fluorescence in situ hybridization.
[a]ISS stage is derived based on the combination of serum ß2-microglobulin and albumin.
[b]Assessed by FISH or karyotyping.
[c]Consists of 2 patients with del17p, 1 patient with t(4;14), and 1 patient with t(14;16).

Pharmacokinetics

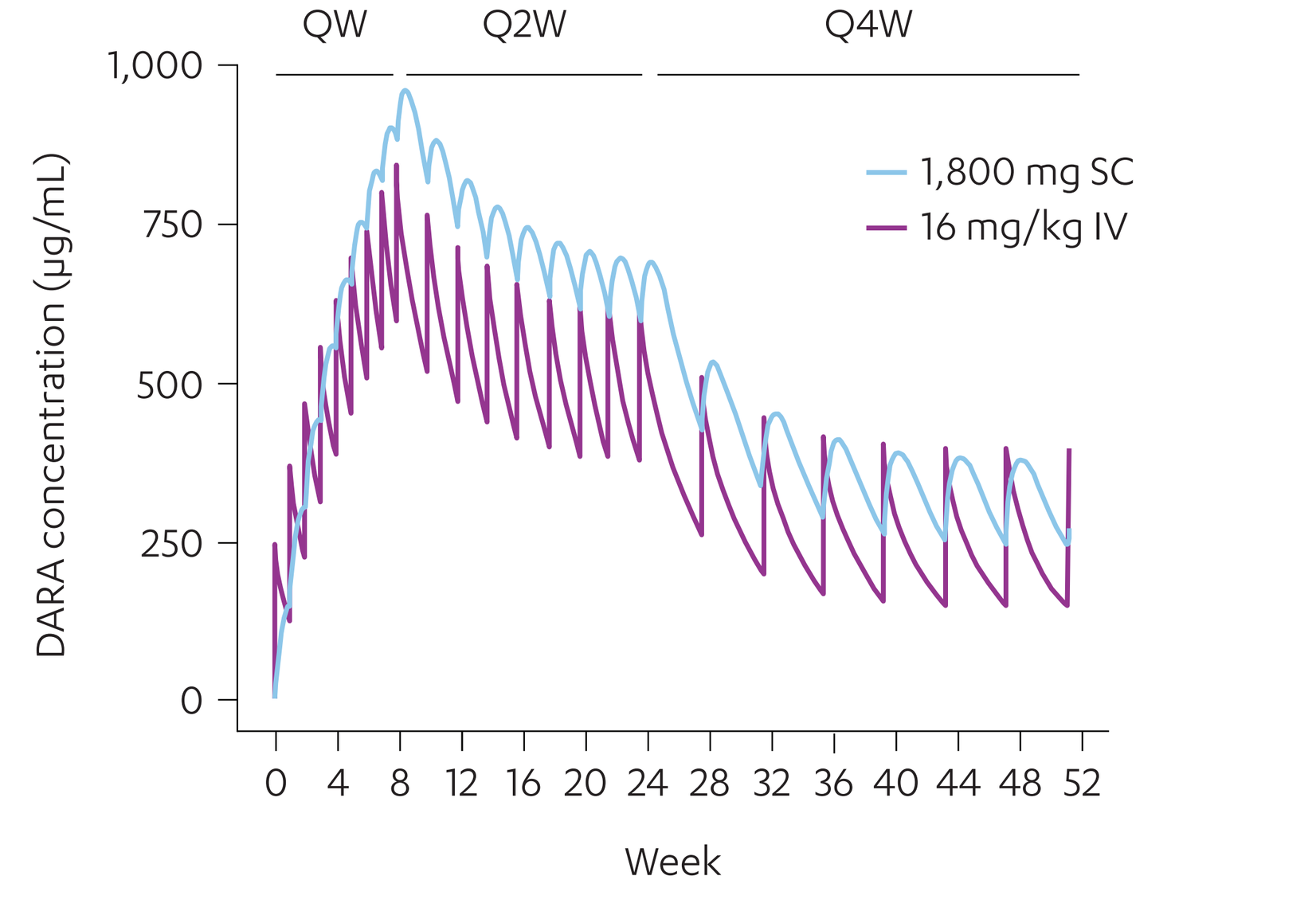
- Mean daratumumab serum concentration profiles revealed the following:
  - SC administration resulted in slower systemic absorption compared with IV administration (**Figure 2A**)
  - Maximum trough concentration (C_{trough}) was similar or higher following 1,800 mg SC compared with 16 mg/kg IV (**Figure 2B** and **Table 2**)
- Simulation of mean concentration-time profiles of daratumumab following SC and IV dosing revealed the following:
  - C_{trough} after 1,800 mg SC dosing remains higher than after 16 mg/kg IV throughout the dosing regimen (**Figure 3**)
  - For SC dosing, mean maximum concentration (C_{max}) is lower during early QW dosing but is higher at the end of QW dosing and during Q2W dosing (**Figure 3**)
  - After reaching Q4W dosing, C_{max} for 1,800 mg SC is similar to that for 16 mg/kg IV overall (**Figure 3**)
- Mean and median C_{trough} values for end of weekly dosing (Cycle 3 Day 1) in PAVO, GEN501 Part 2, and SIRIUS are summarized in **Table 2**



A.
1st dose
DARA concentration (µg/mL)
400
300
200
100
0
0 1 2 12 24 48 72 168 (7 days)
Nominal time after 1st dose (hours)
B.
Last weekly dose (8th dose)
DARA concentration (µg/mL)
1,500
1,000
500
0
0 1 2 24 72 168 (7 days)
Max Ctrough (at C3D1)
Nominal time after last weekly dose (8th dose; hours)
16 mg/kg IV[a]
1,800 mg SC

SD, standard deviation; DARA, daratumumab; C_{trough}, trough concentration; C, Cycle; D, Day; IV, intravenous; SC, subcutaneous.
[a]From the GEN501 study.[17]

Figure 2. Mean (SD) serum concentrations of daratumumab over time after (A) the 1st dose and (B) the last weekly dose (8th dose).



SC, subcutaneous; IV, intravenous; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; DARA, daratumumab.
[a]Dosing schedule is QW in Cycles 1 and 2, Q2W in Cycles 3 through 6, and Q4W thereafter.

Figure 3. Simulation of mean concentration-time profiles of daratumumab following SC and IV dosing.[a]

Table 2. C_{trough} for End of Weekly Daratumumab Dosing (C3D1) in PAVO, GEN501 Part 2, and SIRIUS

			Daratumumab C3D1 C_{trough} (µg/mL)		
Study	Dose/route	n	Mean	Median	CV%
PAVO[a]	1,800 mg SC	22	932	860	42%
GEN501 Part 2	16 mg/kg IV	27	617	714	51%
SIRIUS	16 mg/kg IV	73	573[b]	560	58%

C_{trough}, trough concentration; C, Cycle; D, Day; CV, coefficient of variation; SC, subcutaneously; IV, intravenously.
[a]Based on pharmacokinetic evaluable population.
[b]As reported by Clemens PL, et al.[18]

Safety

- No treatment discontinuations due to treatment-emergent adverse events (TEAEs) were observed (**Table 3**)
- The adverse event profile of DARA SC was consistent with the known profile of DARA IV[12] (**Tables 3** and **4**)

IRRs

- The incidence and severity of IRRs was low with DARA SC
- Among the 25 patients receiving DARA SC, 4 (16%) patients reported IRRs, the majority of which occurred on Day 1
  - Patient 1: hypertension (grade 3), chills (grade 2), dyspnea (grade 2)
  - Patient 2: allergic rhinitis (grade 1)
  - Patient 3: sneezing (grade 1)
  - Patient 4: hypertension (grade 3)
- No discontinuations due to IRRs were observed

Injection-site Reactions

- Few injection-site TEAEs (investigator-reported) were observed with DARA SC
  - Induration, erythema, injection-site discoloration, and hematomas were observed (n = 1 each)
- Measurable erythema (24%) and measurable induration (4%) at the injection site were reversible within 1 hour

Efficacy

- Response rates in the 1,800-mg DARA SC cohort improved with longer follow-up (**Figure 4**)
- Median PFS has not been reached among all-treated patients and also among patients refractory to both PIs and IMiDs

Table 3. Summary of TEAEs

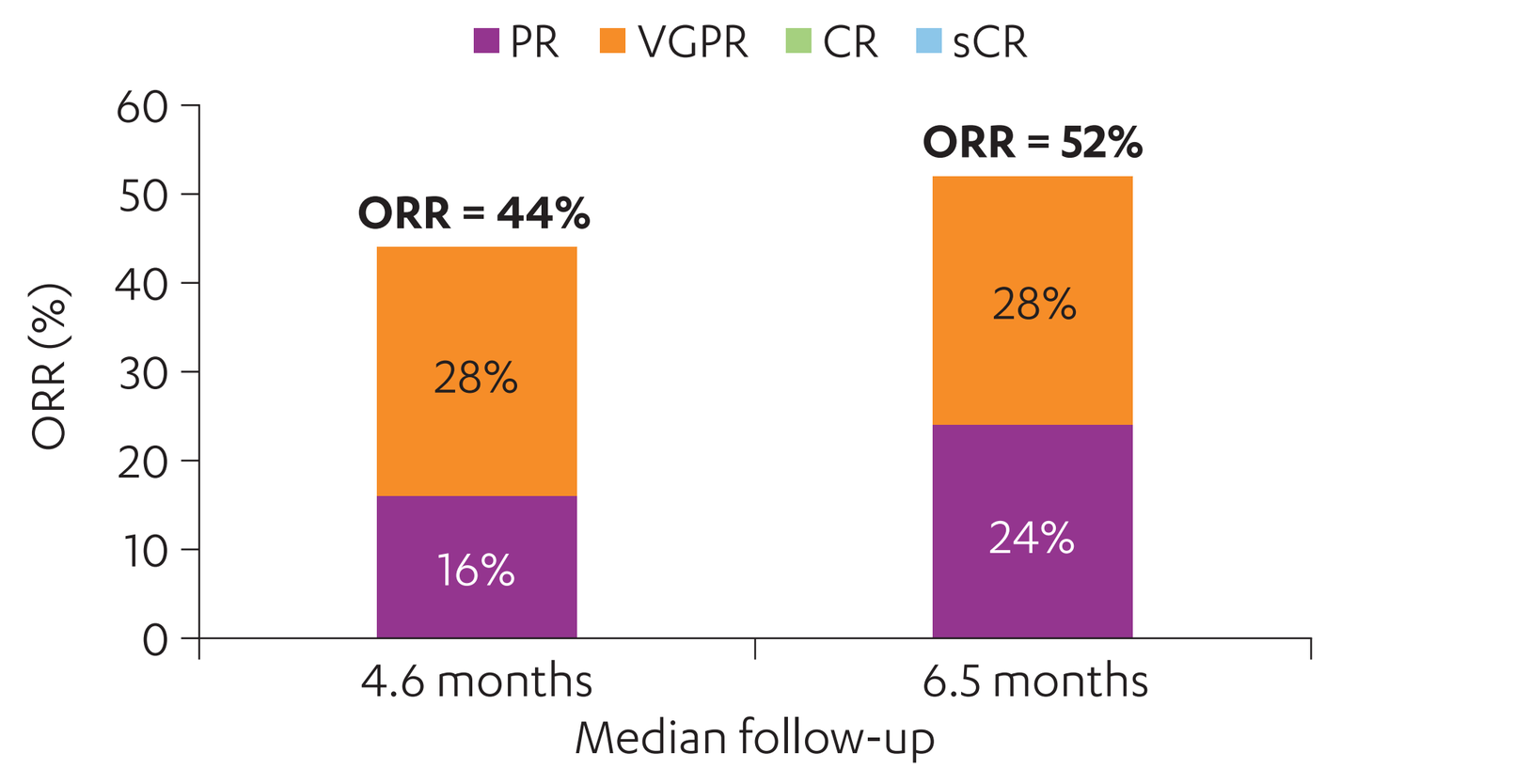
TEAE, n (%)	DARA SC 1,800 mg (n = 25)
Serious TEAE	3 (12)
Grade ≥3 TEAE	12 (48)
Treatment discontinuation due to TEAE	0
All-grade hematologic TEAEs (>10%)	
Lymphopenia	8 (32)
Thrombocytopenia	6 (24)
Anemia	4 (16)
Leukopenia	3 (12)
All-grade nonhematologic TEAEs (>10%)	
Fatigue	5 (20)
Asthenia	5 (20)
Back pain	5 (20)
Diarrhea	5 (20)
Nausea	5 (20)
Headache	5 (20)
Viral upper respiratory tract infection	5 (20)
Pyrexia	4 (16)
Vomiting	4 (16)
Cough	4 (16)
Insomnia	4 (16)
Upper respiratory tract infection	3 (12)
Chills	3 (12)
Peripheral edema	3 (12)
Arthralgia	3 (12)
Musculoskeletal pain	3 (12)

TEAE, treatment-emergent adverse event; DARA, daratumumab; SC, subcutaneous.

Table 4. Summary of Grade 3/4 TEAEs

Grade 3/4 TEAEs (>1 patient), n (%)	DARA SC 1,800 mg (n = 25)
Hematologic	
Lymphopenia	5 (20)
Thrombocytopenia	2 (8)
Neutropenia	2 (8)
Nonhematologic	
Hypertension	2 (8)

TEAE, treatment-emergent adverse event; DARA, daratumumab; SC, subcutaneous.



ORR, overall response rate; DARA, daratumumab; SC, subcutaneous; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.

Figure 4. ORRs in Part 2 (DARA SC 1,800 mg).

CONCLUSIONS

- **DARA co-formulated with rHuPH20 (DARA SC) enables dosing over 3 to 5 minutes**
- **DARA SC 1,800 mg achieves similar or greater maximum C_{trough} compared with standard IV dosing at Cycle 3 Day 1**
- **DARA SC was well tolerated**
  - **The IRR rate with DARA SC was 16%**
    - **IRR rates for DARA IV range from 45% to 56% in RRMM[10-12,19-21]**
- **High clinical response rates that improved with longer follow-up were observed with DARA SC**
- **Median PFS has not been reached after median follow-up of 6.5 months**
- **These data informed the 4 ongoing phase 3 studies of DARA SC 1,800 mg**
  - **COLUMBA (RRMM, DARA SC vs DARA IV; NCT03277105)**
  - **AQUILA (smoldering multiple myeloma, single-agent DARA SC vs active monitoring; NCT03301220)**
  - **APOLLO (RRMM, DARA SC + pomalidomide/dexamethasone [pom-dex] vs pom-dex alone; NCT03180736)**
  - **ANDROMEDA (amyloidosis, DARA SC + bortezomib/cyclophosphamide/dexamethasone [CyBorD] vs CyBorD alone; NCT03201965)**

REFERENCES

1. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
2. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
3. Overdijk MB, et al. *J Immunol*. 2016;197(3):807-813.
4. Lammerts van Bueren J, et al. *Blood*. 2014;124(21):3474.
5. Krejcik J, et al. *Blood*. 2016;128(3):384-394.
6. Adams H III, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 3-6, 2016; San Diego, CA. Abstract 4521.
7. Chiu C, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 3-6, 2016; San Diego, CA. Abstract 4531.
8. DARZALEX® (daratumumab) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc; 2018.
9. European Medicines Agency. Summary of opinion (post authorisation). Darzalex (daratumumab); 2017.
10. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
11. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331.
12. Usmani SZ, et al. *Blood*. 2016;128(1):37-44.
13. Xu XS, et al. *Clin Pharmacol Ther*. 2017;101(6):721-724.
14. Halozyme Therapeutics. www.hylenex.com/mechanism-of-action. Accessed November 2017.
15. Usmani S, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 3-6, 2016; San Diego, CA. Abstract 1149.
16. Chari A, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA. Abstract 838.
17. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
18. Clemens PL, et al. *Clin Pharmacokinet*. 2017;56(8):915-924.
19. Plesner T, et al. *Blood*. 2016;128(14):1821-1828.
20. Chari A, et al. Presented at: Annual Meeting of the American Society of Hematology (ASH); December 3-6, 2016; San Diego, CA. Abstract 2142.
21. Chari A, et al. *Blood*. 2017;130(8):974-981.

ACKNOWLEDGMENTS

The authors thank the patients who participated in this study and their families, the investigators, the staff members involved in data collection and analyses, and Halozyme for their partnership in the study.

This study (NCT02519452) is funded by Janssen Research & Development, LLC. Medical writing and editorial support were provided by Jason Jung, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

DISCLOSURES

AC consulted for Amgen, Array BioPharma, Celgene, Janssen, Millennium, Takeda, and Novartis; and received research funding from Amgen, Array BioPharma, Celgene, Janssen, Millennium, Takeda, Novartis, and Pharmacyclics. SZU consulted for Celgene, Amgen, Takeda, Sanofi, Skyline, Onyx, Millennium, and Janssen; received research funding from Onyx, Sanofi, Array BioPharma, Pharmacyclics, Takeda, Celgene, and Bristol-Myers Squibb; served on speakers bureaus for Celgene, Amgen, and Takeda; provided expert testimony to Janssen and Celgene; and received travel expenses from Janssen, Celgene, Amgen, and Takeda. M-VM received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen. NWCJvdD consulted for Celgene, Janssen, Bristol-Myers Squibb, Amgen, Bayer, Novartis, and Servier; served on a speakers bureau for Janssen; and his institution received research funding from Celgene, Janssen, Bristol-Myers Squibb, and Amgen. JLK consulted for AbbVie, Roche, Takeda, Janssen, and Pharmacyclics; and received research funding from Amgen and Novartis. PM consulted for and received honoraria from Celgene, Takeda, and Janssen. AO consulted for and received honoraria from Amgen, Takeda, and Janssen; and served on speakers bureaus for Amgen and Janssen. TP consulted for Janssen, Takeda, and Genmab; and received research funding from Janssen. LB consulted for and received honoraria from Takeda, Celgene, Janssen, and Amgen; and received travel expenses from Janssen, Celgene, and Amgen. KL, PH, TM, PLC, and AF are employees of Janssen. PLC holds stock and/or stock options in J&J. JS-M consulted for Amgen, Bristol-Myers Squibb, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. HN has no conflicts of interest to report.

POSTER PRESENTED AT THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO); JUNE 1-5, 2018; CHICAGO, ILLINOIS.