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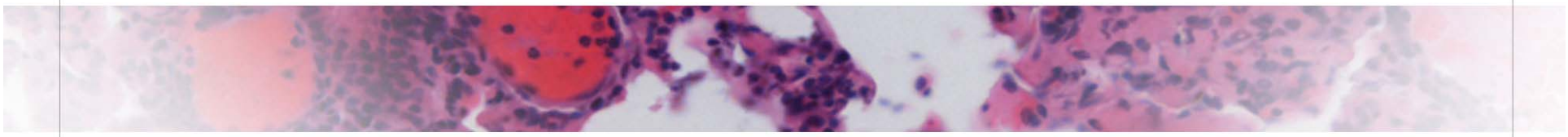

Subcutaneous Delivery of Daratumumab in Patients with Relapsed or Refractory Multiple Myeloma (RRMM): PAVO, an Open-label, Multicenter, Dose Escalation Phase 1b Study

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Background

- DARA 16 mg/kg IV is approved as monotherapy and in combination with Vd, Rd, or Pd in patients with RRMM
- Median duration of the first, second, and subsequent DARA IV infusion was 7.0, 4.3, and 3.5 hours, respectively[1]
- Infusion-related reactions (IRRs) are manageable and occur primarily during the first infusion[2-4]
- Low rates of IRRs with subcutaneous administration of daratumumab have been observed, with short administration time[5]

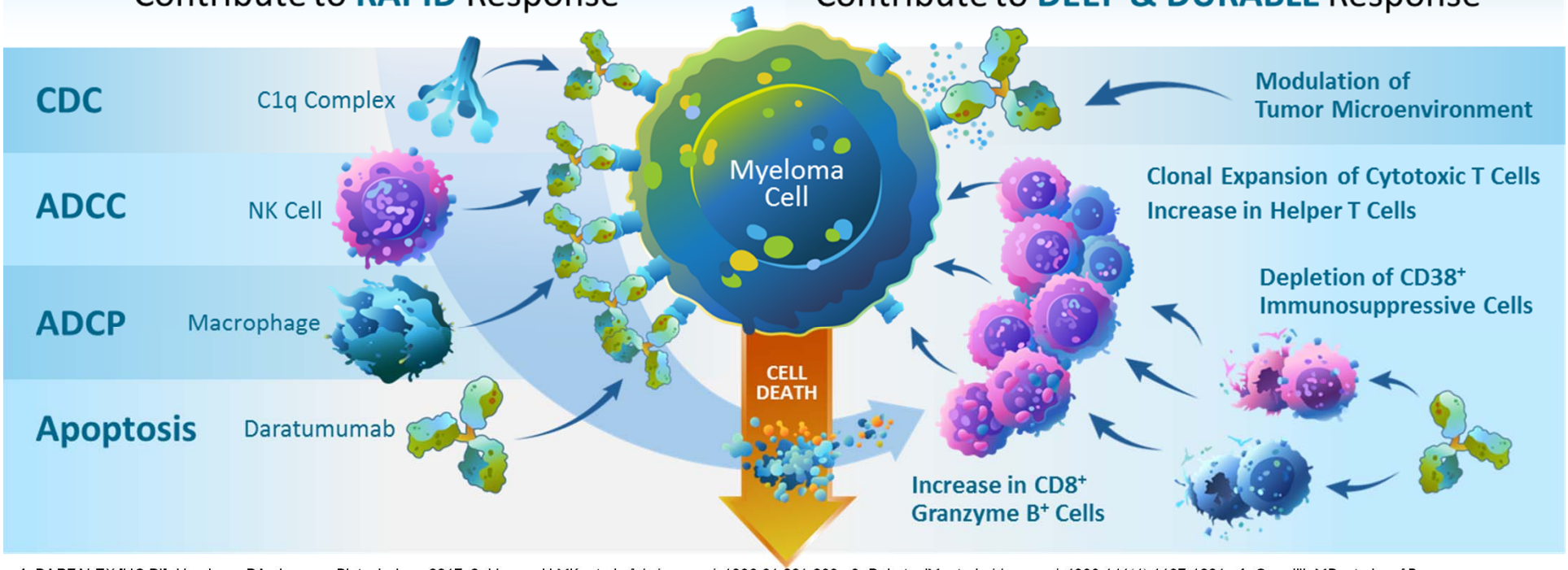
1. DARZALEX (US PI), Horsham, PA: Janssen Biotech, Inc.; 2017.
2. Usmani SZ, et al. *Blood*. 2016;128(1):37-44.
3. Dimopoulos M, et al. *N Engl J Med*. 2016;375(14):1319-1331.
4. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
5. Usmani SZ, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 1149.

DARA, daratumumab; IV, intravenous; Vd, bortezomib and dexamethasone; Rd, lenalidomide and dexamethasone; Pd, pomalidomide and dexamethasone; RRMM, relapsed or refractory multiple myeloma.

Daratumumab's Mechanisms of Action

DIRECT ON-TUMOR Actions may Contribute to RAPID Response[1-6]

IMMUNOMODULATORY Actions may Contribute to DEEP & DURABLE Response[1,7-9]



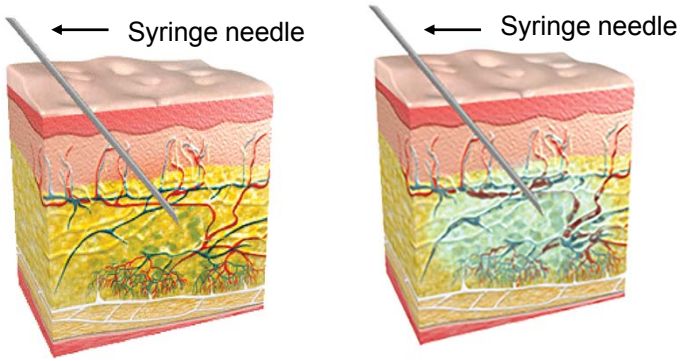
1. DARZALEX [US PI], Horsham, PA: Janssen Biotech, Inc.; 2017. **2.** Liszewski MK, et al. *Adv Immunol*. 1996;61:201-283. **3.** Debets JM, et al. *J Immunol*. 1988;141(4):1197-1201. **4**. Overdijk MB, et al. *mABs*. 2015;7(2):311-321. **5.** Lokhorst HM, et al. *NEJM*. 2015;373(13):1207-1219. **6.** Plesner T, et al. Oral presentation at: ASH; December 8-11, 2012; Atlanta, GA **7**. Krejcik J, et al. *Blood*. 2016;128(3):384-394. **8**. Adams H, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. **9**. Chiu C, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA.

CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis.

Recombinant Human Hyaluronidase

- ENHANZE™ Drug Delivery Technology of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid administration of larger volumes of injected drugs[1]
- Mixed formulation of DARA and rHuPH20 (DARA-MD) given subcutaneously by means of **syringe pump** was well tolerated with low rates of IRRs and similar efficacy to IV DARA[2]
- Pre-mixed co-formulation of DARA + rHuPH20 (DARA SC) with a higher DARA concentration, lower injection volume, and shorter injection time was developed, enabling **manual subcutaneous** injection in the abdomen

Schematic of rHuPH20[1]



Aim: To determine the safety, pharmacokinetics, and efficacy of subcutaneous DARA

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed 11/8/2016.
2. Usmani SZ, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 1149.

PAVO Study Design

Phase 1b, open-label, multicenter, dose-finding, proof-of-concept study

Key eligibility criteria
- RRMM with measurable disease
- ≥2 prior lines of treatment
- Not received anti-CD38 therapy

Part 1: mix and deliver

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
- C_{trough} of DARA at Cycle 3/Day1
- Safety

Secondary endpoints
- ORR
- CR
- Duration of response
- Time to response

Infusion/injection time
- DARA-MD 1,200 mg: 20-min via pump (60 mL)
- DARA-MD 1,800 mg: 30-min via pump (90 mL)
- **DARA SC 1,800 mg: 3-5 min manually (15 mL)**

Dosing schedule
- Approved schedule for IV
- 1 Cycle = 28 days

Pre-[b]/post-administration medication
- Acetaminophen
- Diphenhydramine
- Montelukast
- Methylprednisolone[c]

[a]Group 2 comprises 4 distinct cohorts, each treated with DARA 1,800 mg and rHuPH20 45,000 U. 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 PK after Cycle 3/Day 1 for each group.
[b]Administered 1 to 3 hours prior to injection. [c]100 mg for the first and second injections; dose may be reduced to 60 mg thereafter; 20 mg for post-administration over 2 days. In the absence of infusion related AEs after the first 3 injections, postinjection corticosteroids should be administered per investigator discretion.

RRMM, relapsed or refractory multiple myeloma; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response.

Baseline Demographics and Clinical Characteristics

Characteristic	Part 1 (DARA-MD) 1,200 mg n = 8	Part 1 (DARA-MD) 1,800 mg n = 45	Part 2 (DARA SC) 1,800 mg n = 25
Age, y			
Median (range)	66 (49-78)	63 (36-79)	68 (51-85)
≥75, n (%)	1 (13)	4 (9)	6 (24)
Median (range) weight, kg	75.0 (53.0-82.5)	74.8 (48.0-133.0)	70.9 (52.0-104.8)
Baseline ECOG status, n (%)			
0	2 (25)	11 (24)	11 (44)
1	5 (63)	33 (73)	13 (52)
2	1 (13)	1 (2)	1 (4)
ISS stage at screening, n (%)[a]			
N	6	45	24
I	1 (17)	21 (47)	13 (54)
II	3 (50)	15 (33)	5 (21)
III	2 (33)	9 (20)	6 (25)
Median (range) time from diagnosis, y	6.55 (1.9-10.3)	5.94 (1.1-15.2)	5.96 (2.1-13.2)
Type of myeloma, N	8	45	24
IgG, n (%)	3 (38)	30 (67)	13 (54)

[a]ISS stage is derived based on the combination of serum β2-microglobulin and albumin.
ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

Baseline Demographics and Clinical Characteristics

Characteristic	Part 1 (DARA-MD) 1,200 mg n = 8	Part 1 (DARA-MD) 1,800 mg n = 45	Part 2 (DARA SC) 1,800 mg n = 25
Prior lines of therapy, n (%)			
Median (range)	5 (2-10)	4 (2-11)	3 (2-9)
≤3	3 (38)	16 (36)	16 (64)
>3	5 (63)	29 (64)	9 (36)
Prior ASCT, n (%)	5 (63)	37 (82)	17 (68)
Prior PI, n (%)	8 (100)	45 (100)	25 (100)
Prior bortezomib	8 (100)	43 (96)	24 (96)
Prior IMiD, n (%)	8 (100)	45 (100)	25 (100)
Prior lenalidomide	8 (100)	45 (100)	23 (92)
Refractory to, n (%)			
PI only	0 (0)	1 (2)	3 (12)
IMiD only	1 (13)	7 (16)	2 (8)
Both PI and IMiD	5 (63)	29 (64)	15 (60)
Last line of therapy	7 (88)	36 (80)	19 (76)

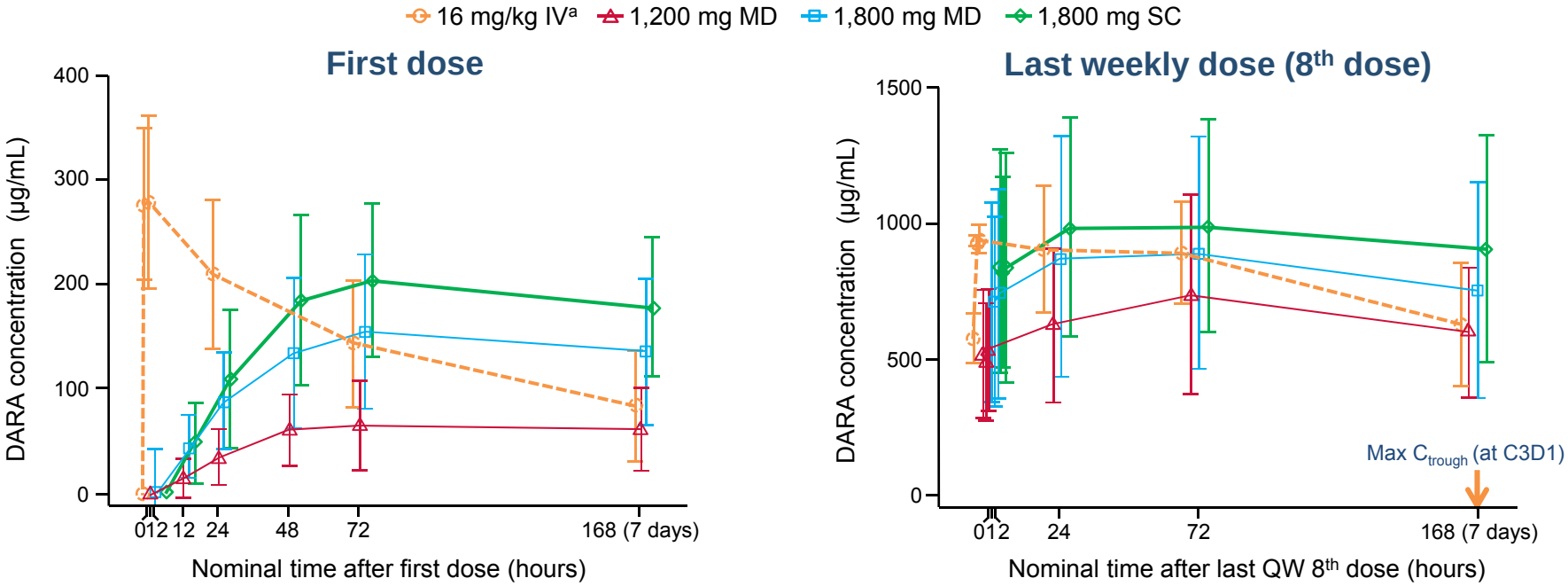
ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.

Patient Disposition

- Clinical cut-off date: Oct 30, 2017

	Part 1: DARA-MD		Part 2: DARA SC
	1,200 mg n = 8	**1,800 mg n = 45**	**1,800 mg n = 25**
Patients treated, n	8	45	25
Patients who discontinued treatment, n (%)	8 (100)	35 (78)	5 (20)
Reason for discontinuation			
Progressive disease	5 (63)	28 (62)	4 (16)
Withdrawal by patient	1 (13)	1 (2)	0 (0)
Physician decision	1 (13)	5 (11)	1 (4)
Death	1 (13)	1 (2)	0 (0)
Median (range) duration of follow up, mo:	**5.2** (1.6-13.9)	**8.3** (1.8-19.5)	**4.6** (2.4-5.5)

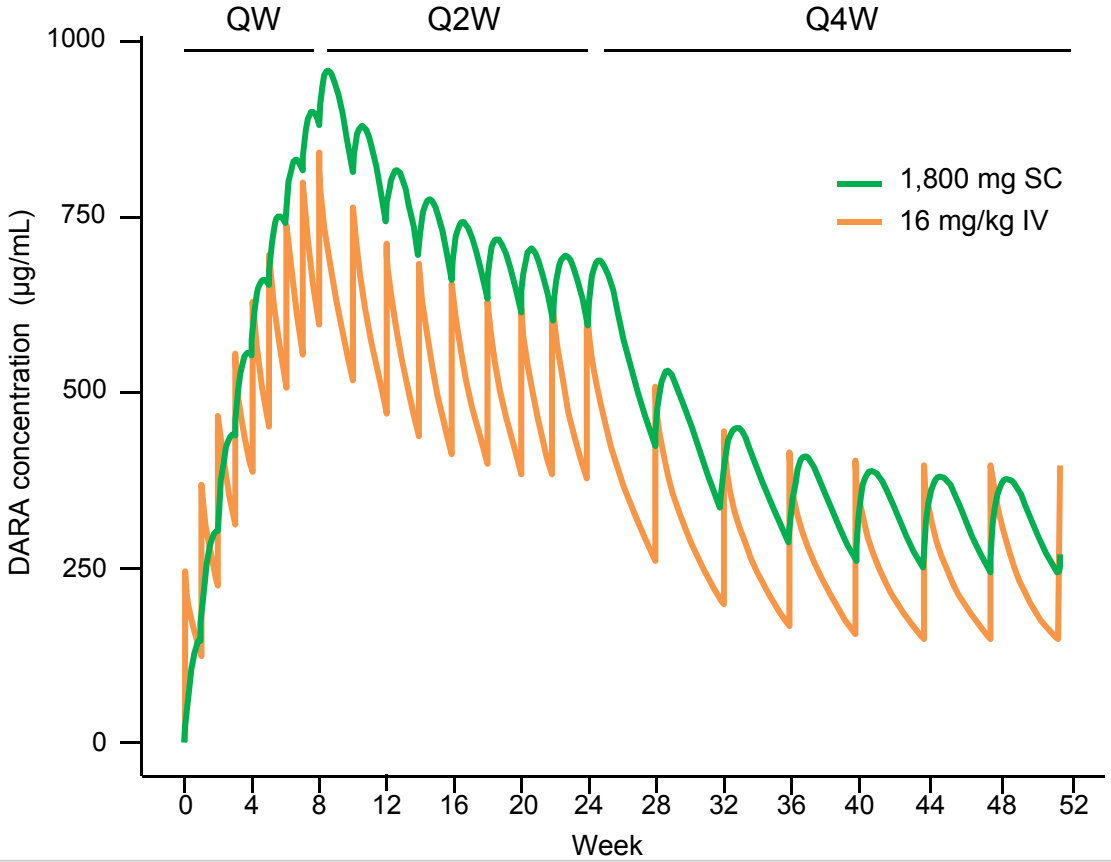
Mean (SD) DARA Serum Concentration Profiles



- **SC administration results in slower systemic absorption compared with IV**
- **Maximum C_{trough} is similar or higher following 1800 mg SC compared with 16 mg/kg IV**

[a]From study GEN501.
QW, once weekly.

Simulation of Mean Concentration-Time Profiles[a]



- C_{trough} following 1,800 mg SC dosing remains higher than 16 mg/kg IV throughout dosing regimen
- Mean C_{max} starts lower during early QW dosing with SC dosing, but is higher at the end of QW dosing and during Q2W dosing
- After reaching Q4W dosing, C_{max} for 1,800 mg SC is similar to 16 mg/kg IV overall

[a]Dosing schedule is once weekly in Cycles 1 to 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks thereafter.
C_{max}, peak plasma concentration; Q2W, every 2 weeks; Q4W, every 4 weeks.

Summary of Safety Events: DARA SC

	Part 1 (DARA-MD)		Part 2 (DARA SC)
TEAE, n (%)	**1,200 mg n = 8**	**1,800 mg n = 45**	**1,800 mg n = 25**
Drug-related TEAE	5 (63)	31 (69)	12 (48)
Serious drug-related TEAE	1 (13)	3 (7)	0
Grade ≥3 TEAE	5 (63)	22 (49)	10 (40)
All-grade hematologic TEAEs >25%			
Thrombocytopenia	3 (38)	8 (18)	5 (20)
Anemia	2 (25)	15 (33)	3 (12)
Lymphopenia	0	8 (18)	7 (28)
All-grade nonhematologic TEAEs >25%			
Upper respiratory tract infection	3 (38)	11 (24)	2 (8)
Decreased appetite	3 (38)	3 (7)	2 (8)
Insomnia	3 (38)	5 (11)	4 (16)
Pyrexia	2 (25)	12 (27)	4 (16)
Median duration of treatment:	**2.6 months**	**5.4 months**	**4.6 months**

- No TEAE-related treatment discontinuations

TEAE, treatment-emergent adverse event.

Grade 3/4 TEAEs: DARA SC

	DARA-MD		DARA SC
Grade 3/4 TEAE (>1 patient), n (%)	**1,200 mg n = 8**	**1,800 mg n = 45**	**1,800 mg n = 25**
Hematologic			
Anemia	1 (13)	7 (16)	1 (4)
Lymphopenia	0 (0)	5 (11)	4 (16)
Thrombocytopenia	1 (13)	3 (7)	2 (8)
Neutropenia	1 (13)	3 (7)	2 (8)
Nonhematologic			
Fatigue	2 (25)	1 (2)	1 (4)
Hypertension	2 (25)	2 (4)	1 (4)
Hyponatremia	0 (0)	2 (4)	1 (4)
Pneumonia	1 (13)	2 (4)	0
Device related infection	0	2 (4)	0
Respiratory syncytial virus infection	0	2 (4)	0
Median duration of treatment:	**2.6 months**	**5.4 months**	**4.6 months**

AE profile of DARA subcutaneous is consistent with DARA IV

IRRs: DARA SC

- 3/25 (12%) patients in DARA SC reported IRRs, all at first injection (within 6 h)
  - Patient 1: Hypertension (G3), chills (G2), dyspnea (G2)
  - Patient 2: Allergic rhinitis (G1)
  - Patient 3: Sneezing (G1)
- No grade 4 IRRs were reported
- No discontinuations due to IRRs
- No delayed occurrences of IRRs

Low IRR incidence and severity with subcutaneous DARA

IRR, infusion-related reaction.

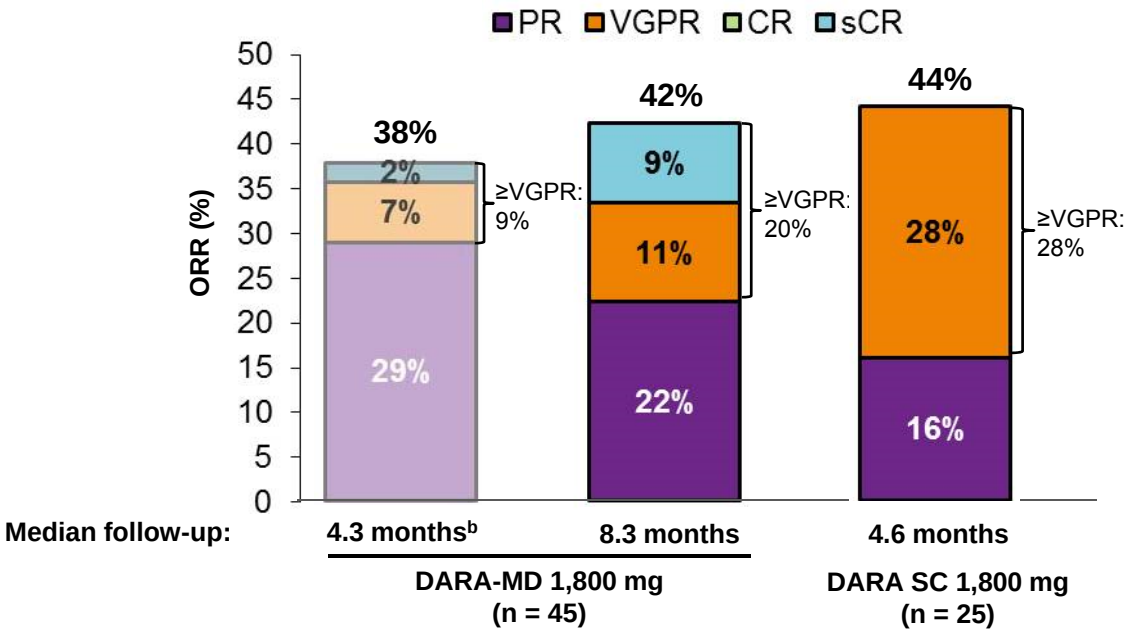
Injection-site Reactions: DARA SC

	Part 2 (DARA SC)
	1,800 mg (15 mL / 3-5 min) n = 25
Injection site TEAEs (investigator reported), n (%)[a]	
Induration	1 (4)
Erythema	1 (4)
Injection-site discoloration	1 (4)
Hematoma	1 (4)
Injection site measurements, n (%)	
Erythema	5 (20)

- **Few injection-site TEAEs with subcutaneous DARA**
- **Measurable erythema was reversible within 1 hour**

[a]All grade 1 in severity.

ORR[a]: 1,800 mg Groups



- **Deepening responses observed in the 1,800-mg DARA-MD group**
- **1,800-mg DARA SC demonstrates similar response rates as 1,800-mg DARA-MD**

[a]Response-evaluable set; [b]Data presented by Usmani SZ, et al. Presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 1149.

PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.

Conclusions

- DARA co-formulated with recombinant human hyaluronidase (DARA SC) enables dosing in 3 to 5 minutes
- DARA SC 1,800 mg achieves greater maximum C_{trough} compared with standard IV dose at C3D1
- DARA SC was well tolerated
  - Rate of IRRs with DARA SC was 12%; IRRs for DARA IV range between 45%-56% in RRMM[1-6]
- Clinical responses with DARA SC were observed, with rates similar to DARA-IV

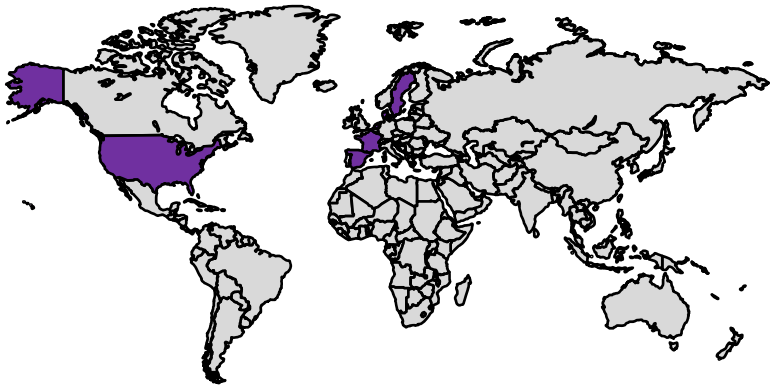
These data informed the four ongoing phase 3 studies[a] using DARA SC 1,800 mg

[a]COLUMBA (DARA SC vs IV), AQUILA (smoldering MM, single agent), APOLLO (DARA SC + pom/dex), and ANDROMEDA (amyloidosis, DARA SC + VCd).

1. Usmani S, et al. *Blood.* 2016;128(1):37-44. 2. Plesner T, et al. *Blood.* 2016;128(14):1821-1828. 3. Chari A, et al. Poster presented at: ASH; December 3-6, 2016; San Diego, CA. Abstract 2142. 4. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-66. 5. Dimopoulos MA, et al. *N Engl J Med*. 2016;375(14):1319-1331. 6. Chari A, et al. *Blood*. 2017; 130(8): 974–981.

Acknowledgments

- **Patients who participated in this study and their families**
- Investigators
- Staff members involved in data collection and analyses
- Halozyme for their partnership with the study



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Backup

Additional TEAEs of Interest

- Neutropenia
  - DARA-MD 1,200 mg: 1 (13%) patient had grade 4 neutropenia
  - DARA-MD 1,800 mg: 7 (16%) patients; one grade 3 and two grade 4 neutropenias
  - DARA SC 1,800 mg: 2 (8%) patients; both grade 3 neutropenia
- Infections
  - DARA-MD 1,200 mg: 7 (88%) patients; two grade 3 and one grade 4 infections
  - DARA-MD 1,800 mg: 31 (70%) patients; 7 (16) patients had grade 3 infections
  - DARA SC 1,800 mg: 11 (44%) patients; all grade 1 or 2 infections
- Injection site reactions
  - DARA-MD 1,200 mg: Erythema (5 [63%] patients); Induration (4 [50%] patients)
  - DARA-MD 1,800 mg: Erythema (13 [29%] patients); Induration (10 [22%] patients)
  - DARA SC 1,800 mg: Erythema (6 [24%] patients); Induration (1 [4%] patients)

Timing of Grade 3/4 TEAE Onset

	Part 1 (DARA-MD)		Part 2 (DARA SC)
	1,200 mg n = 8	1,800 mg n = 45	1,800 mg n = 25
Hematologic TEAEs, day of onset			
Anemia	1	2, 2, 3, 4, 23, 56, 85, 97	3
Thrombocytopenia	57	8, 23	15, 22
Neutropenia	20	8, 4, 50	29, 52
Febrile neutropenia		21	46
Lymphopenia		8, 11, 15, 98, 149	3, 8, 8, 9
Leukopenia		7	45
Infections, day of onset			
Pneumonia	37, 84	59, 146	
Staphylcoccal infection	71		
Upper respiratory tract infection	116		
Urinary tract infection	26	23	
Influenza	135		
Sepsis	37		
Lung infection		241	
Device related infection		23, 48	
Respiratory syncytial virus infection		196, 203	

Note: red font indicates grade 4 TEAEs.