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)

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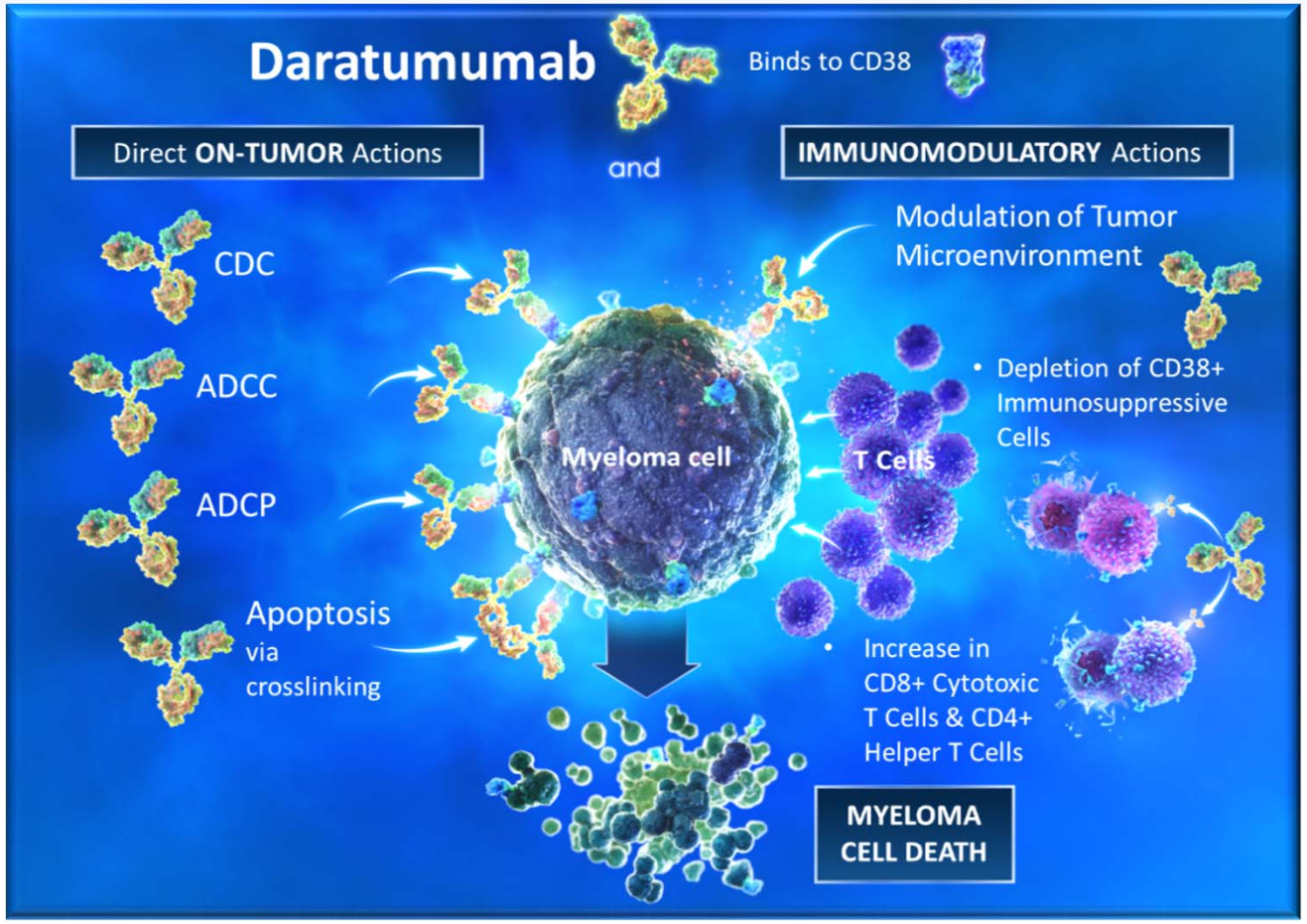
Daratumumab: Mechanism of Action

- Daratumumab (DARA) is a human monoclonal antibody that targets CD38 with a direct on-tumor and immunomodulatory mechanism of action (MoA)[1-5]



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

1. Lammerts van Bueren J, et al. *Blood*. 2014;124. Abstract 3474.
2. Overdijk MB, et al. *J Immunol*. 2016;197(3):807-813.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Krejcik J, et al. *Blood*. 2016;128(3):384-394.

Background

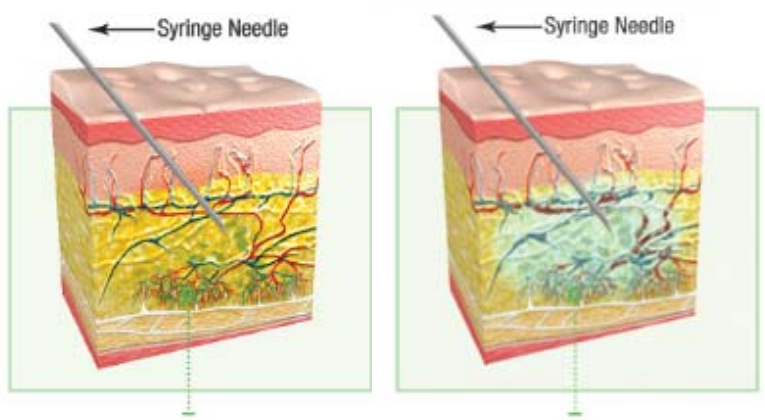
- DARA 16 mg/kg IV monotherapy is approved in the United States, Europe, Canada, Singapore, and Mexico
  - DARA IV in combination with standard of care regimens is approved in the United States
- Intravenous (IV) DARA achieves rapid, deep, and durable responses with significant clinical benefit as monotherapy and when combined with established standard of care[1-3]
- The median duration of first, second, and subsequent IV infusions was 7.0, 4.2, and 3.4 hours, respectively[4]
- DARA IV–associated infusion-related reactions (IRRs) are manageable, and the majority (92%-96%) occur during the first infusion[1-3]

1. Usmani SZ, et al. *Blood*. 2016;128(1):37-44.
2. Dimopoulos M, et al. *N Engl J Med*. 2016;375(14):1319-1331.
3. Palumbo A, et al. *N Engl J Med*. 2016;375(8):754-766.
4. Lonial S, et al. *Lancet*. 2016;387:1551-60.

Recombinant Human Hyaluronidase

- ENHANZE™ platform of recombinant human hyaluronidase (rHuPH20) temporarily breaks down the hyaluronan barrier, allowing rapid absorption of injected drugs[1]
- Herceptin SC® and MabThera SC® are approved in Europe as co-formulate products with rHuPH20[2,3]
  - Dosing time is 5 to 8 minutes with SC versus 0.5 to 6 hours with IV[4-6]

Schematic of rHuPH20[1]



Aim: To determine the safety, pharmacokinetics, and efficacy of DARA as SC administration

1. Halozyme Therapeutics. Mechanism of action for Hylenex recombinant (hyaluronidase human injection). www.hylenex.com/mechanism-of-action. Accessed 11/8/2016.
2. European Medicines Agency. Herceptin: EPAR – product information. 2016
3. European Medicines Agency. MabThera: EPAR – product information. 2016.
4. Ismael G, et al. *Lancet Oncology*. 2012;13(9):869-878.
5. Shpilberg O, et al. *Br J Cancer*. 2013;109(6):1556-1561.
6. De Cock E, et al. *Plos One*. 2016;11(6):e0157957.

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

Group 1 (n = 8)
DARA: 1,200 mg
rHuPH20: 30,000 U

→

Group 2[a] (n = 45)
DARA: 1,800 mg
rHuPH20: 45,000 U

Primary endpoints
- C_{trough} of DARA at Cycle 3/Day 1
- Safety

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

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

Infusion time
- 1,200 mg: 20-min infusion (60 mL)
- 1,800 mg: 30-min infusion (90 mL)

Pre-[b]/post-infusion medication
- Acetaminophen, diphenhydramine, montelukast, and methylprednisolone

RRMM, relapsed or refractory multiple myeloma; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; C_{trough}, trough concentration; ORR, overall response rate; CR, complete response; PK, pharmacokinetic.
[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 hour prior to infusion.

Baseline Demographic and Clinical Characteristics

Characteristic	1,200 mg n = 8	1,800 mg n = 45
Age, y		
Median (range)	**66** (49-78)	**63** (36-79)
≥75, % (n)	**13** (1)	**9** (4)
Median (range) weight, kg	**75.0** (53.0-82.5)	**74.8** (48.0-133.0)
Baseline ECOG status, % (n)		
0	**25** (2)	**24** (11)
1	**63** (5)	**73** (33)
2	**13** (1)	**2** (1)
ISS stage, % (n)[a,b]		
I	**17** (1)	**47** (21)
II	**50** (3)	**33** (15)
III	**33** (2)	**20** (9)
Median (range) time from diagnosis, y	**6.55** (1.9-10.3)	**5.94** (1.1-15.2)

Characteristic	1,200 mg n = 8	1,800 mg n = 45
Prior lines of therapy, % (n)		
Median (range)	**5** (2-10)	**4** (2-11)
≤3	**38** (3)	**36**(16)
>3	**63** (5)	**64** (29)
Prior ASCT, %	**63** (5)	**82** (37)
Prior PI, %	**100** (8)	**100** (45)
Prior bortezomib	**100** (8)	**96** (43)
Prior IMiD, %	**100** (8)	**100** (45)
Prior lenalidomide	**100** (8)	**100** (45)
Refractory to, %		
PI only	**0** (0)	**4** (2)
IMiD only	**13** (1)	**20** (9)
Both PI and IMiD	**63** (5)	**58** (26)
Last line of therapy	**88** (7)	**71** (32)

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; ASCT, autologous stem cell transplantation; PI, proteasome inhibitor; IMiD, immunomodulatory drug.
[a]ISS stage is derived based on the combination of serum β2-microglobulin and albumin.
[b]n = 6 for the 1,200-mg group.

Patient Disposition

- Clinical cut-off date: November 15, 2016
- Median (range) follow-up
  - 1,200 mg: 6.4 (1.6-12.0) months
  - 1,800 mg: 4.3 (0.8-8.6) months
- Median (range) duration of treatment
  - 1,200 mg: 2.6 (0.7-12.0) months
  - 1,800 mg: 3.4 (0.7-8.6) months

	1,200 mg n = 8	1,800 mg n = 45
Patients treated, n	**8**	**45**
Patients who discontinued treatment, % (n)	**88** (7)	**33** (15)
Reason for discontinuation		
Progressive disease	**63** (5)	**27** (12)
Withdrawal by patient	**13** (1)	**0** (0)
Physician decision	**0** (0)	**4** (2)
Death	**13** (1)	**2** (1)

Summary of Safety Events

TEAE	1,200 mg n = 8	1,800 mg n = 45
Drug-related TEAE, % (n)	**63** (5)	**62** (28)
Serious drug-related TEAE, % (n)	**13** (1)	**7** (3)
Grade ≥3 TEAE, % (n)	**63** (5)	**40** (18)
All-grade hematologic TEAEs >25%, % (n)		
Anemia	**25** (2)	**31** (14)
Thrombocytopenia	**38** (3)	**18** (8)
All-grade nonhematologic TEAEs >25%, % (n)		
Upper respiratory tract infection	**38** (3)	**9** (4)
Insomnia	**38** (3)	**9** (4)
Decreased appetite	**38** (3)	**7** (3)

- No treatment discontinuations due to TEAEs were observed in the 1,800-mg group

AE profile of DARA-PH20 was consistent with IV DARA

TEAE, treatment-emergent adverse event; AE, adverse event; DARA-PH20, daratumumab in combination with recombinant human hyaluronidase.

Grade 3/4 TEAEs

Grade 3/4 TEAEs (>1 patient)	1,200 mg n = 8	1,800 mg n = 45
Hematologic, % (n)		
Anemia	**13** (1)	**13** (6)
Thrombocytopenia	**13** (1)	**7** (3)
Neutropenia	**13** (1)	**7** (3)
Lymphopenia	**0** (0)	**7** (3)
Nonhematologic, % (n)		
Hypertension	**25** (2)	**4** (2)
Fatigue	**25** (2)	**2** (1)
Device-related infection	**0** (0)	**4** (2)
Hyponatremia	**0** (0)	**4** (2)

AE profile of DARA-PH20 was consistent with IV DARA

IRRs

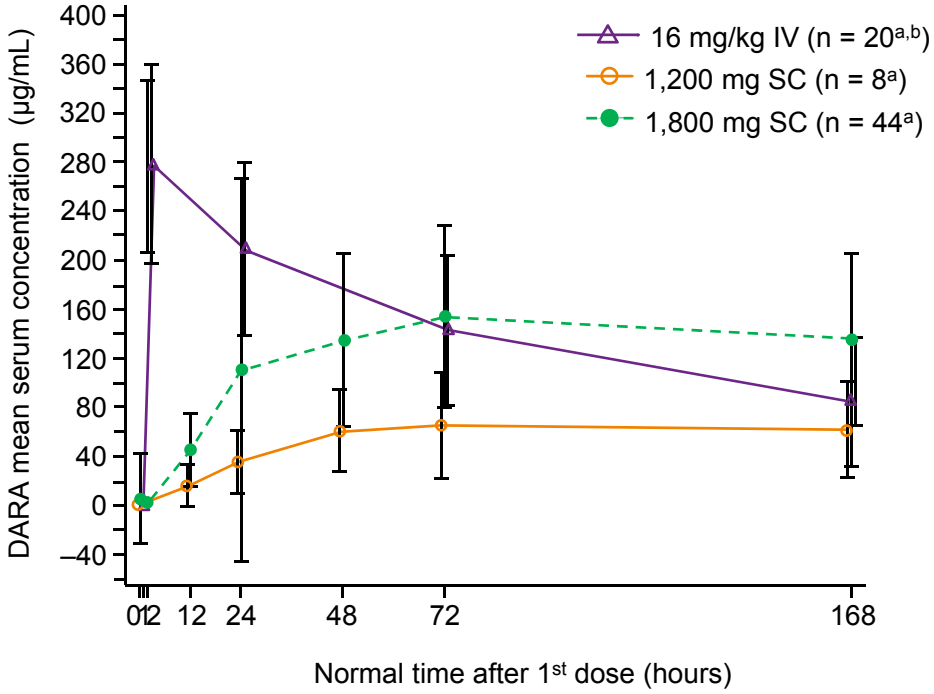
	1,200 mg n = 8	1,800 mg n = 45
IRR, % (n)	**13** (1)	**24** (11)
Chills	**13** (1)	**9** (4)
Pyrexia	**0** (0)	**9** (4)
Pruritus	**0** (0)	**4** (2)
Dyspnea	**13** (1)	**0** (0)
Flushing	**0** (0)	**2** (1)
Hypertension	**0** (0)	**2** (1)
Hypotension	**0** (0)	**2** (1)
Nausea	**0** (0)	**2** (1)
Non-cardiac chest pain	**13** (1)	**0** (0)
Oropharyngeal pain	**0** (0)	**2** (1)
Paresthesia	**0** (0)	**2** (1)
Rash	**0** (0)	**2** (1)
Sinus headache	**0** (0)	**2** (1)
Tongue edema	**0** (0)	**2** (1)
Vomiting	**0** (0)	**2** (1)
Wheezing	**0** (0)	**2** (1)

- All IRRs in the 1,800-mg group were grade 1 or 2
- One grade 3 IRR of dyspnea in the 1,200-mg group
- No grade 4 IRRs were observed
- All IRRs occurred during or within 4 hours of the first infusion
- No IRRs occurred during subsequent infusions in either group
- Abdominal wall SC injections were well tolerated

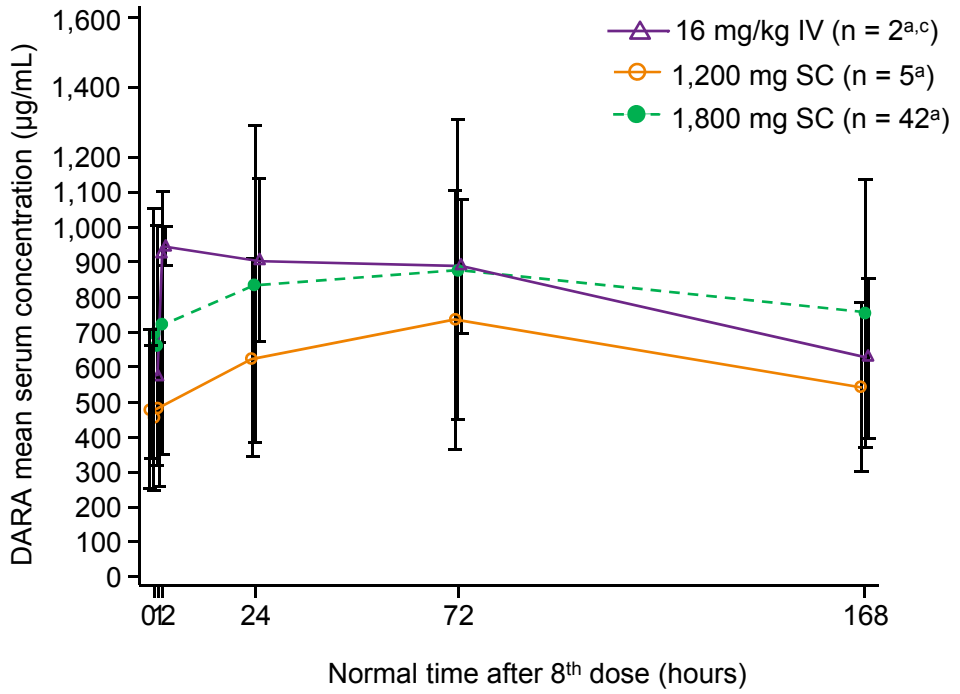
Low IRR incidence and severity with DARA SC

Dose Mean (SD) Profiles

1st dose mean



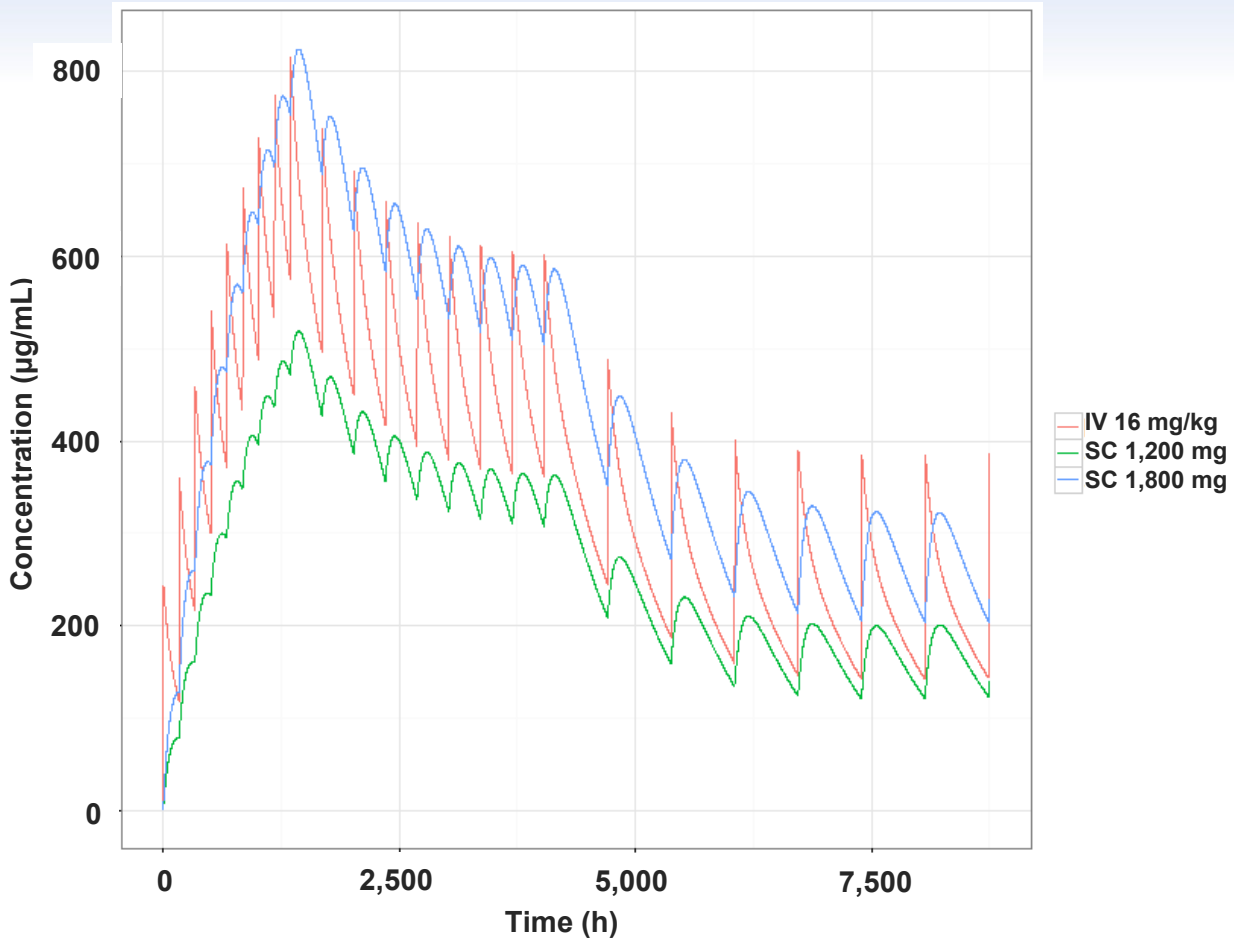
8th dose mean



PK for 1,800 mg SC dose is consistent with the 16 mg/kg IV dose, with comparable C_{trough} and variability

SD, standard deviation.
[a]Number of patients with full PK profile at pre-dose.
[b]From study GEN501 Part 2.
[c]From study GEN501 Part 1.

Simulation of Mean Concentration-Time Profiles of DARA Following SC and IV Dosing[a]

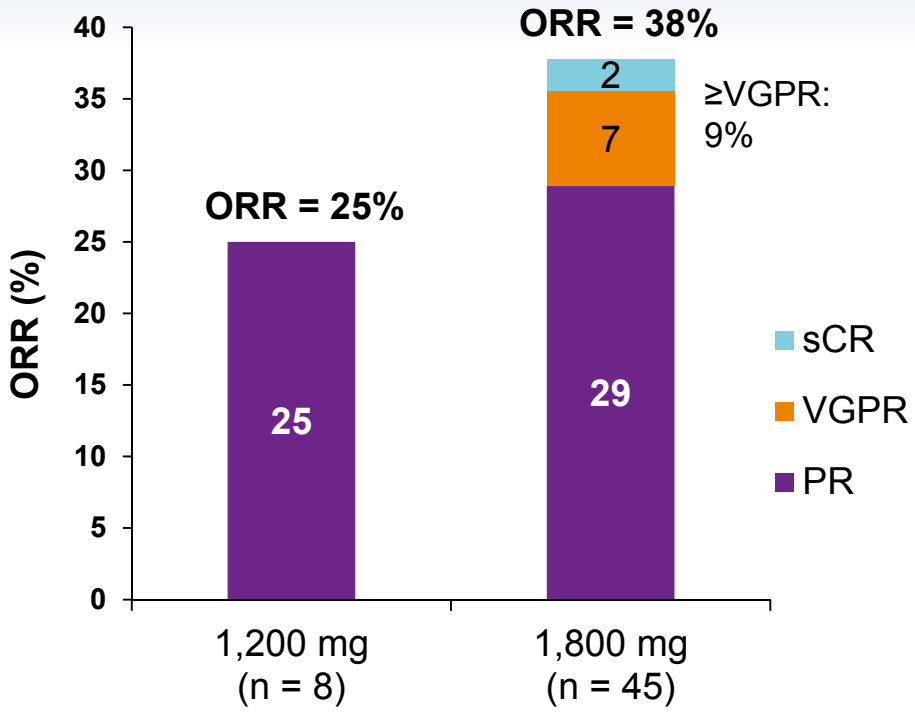


- Similar C_{max} for SC 1,800 mg versus IV 16 mg/kg overall
- Lower C_{max} for SC 1,800 mg during the initial weekly administration
- Higher C_{trough} for SC 1,800 mg versus SC 1,200 mg

C_{max}, peak plasma concentration.
[a]Dosing schedule is QW in Cycles 1 to 2, Q2W in Cycles 3 to 6, and Q4W thereafter.

ORR

Response	1,200 mg n = 8	1,800 mg n = 45
ORR, % (n)	**25** (2)	**38** (17)
sCR	**0** (0)	**2** (1)
CR	**0** (0)	**0** (0)
VGPR	**0** (0)	**7** (3)
PR	**25** (2)	**29** (13)
MR	**13** (1)	**11** (5)
SD	**50** (4)	**38** (17)
PD	**13** (1)	**13** (6)



- Responses to DARA-PH20 were observed across both groups

Deeper responses were observed in the 1,800-mg group

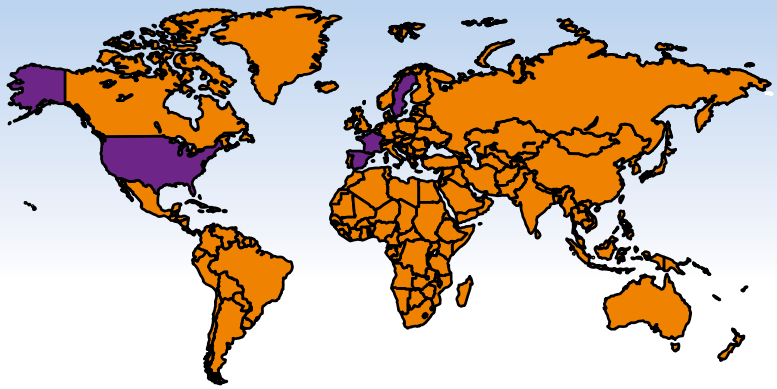
Response-evaluable set.
sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.

Conclusions

- DARA can be combined safely with rHuPH20
- SC DARA was well tolerated with low IRR rates
  - SC injections were well tolerated
- PK profile of the 1,800-mg dose was consistent with DARA 16 mg/kg IV
- Efficacy was consistent with IV DARA in a similar patient population
  - 38% ORR, including deep responses (1 sCR)

Tolerability, safety, and PK data support continued development of SC DARA in different settings

Acknowledgments



6 countries

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

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Backup Slide

C_{trough} of DARA on Cycle 3/Day 1

Study	Dose/route	n	Mean trough (µg/mL)	%CV
GEN501 Part 2	16 mg/kg IV	27	617.17	51%
SIRIUS[1]	16 mg/kg IV	73	573.49	58%
PAVO	**1,200 mg SC** **1,800 mg SC**	**5** **39**	**510.46** **714.00**	**47%** **50%**

- Mean C_{trough} was higher in the 1,800-mg group compared with the 1,200-mg group
- Variability (%CV) was similar between SC DARA and IV DARA 16 mg/kg

CV, coefficient of variation.
Analysis includes all subjects with a concentration value at the Cycle 3/Day 1 trough time point, regardless of missed doses. Cycle 3/Day 1 represents the end of weekly dosing.
1. Clemens P, et al. *Clin Pharmacokinet*. 29 Nov 2016. Epub ahead of print.