Rapid and Robust Mobilization of CD34⁺ HSCs without G-CSF Following Administration of MGTA-145 Alone or in Combination with Plerixafor

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BACKGROUND

Most hematopoietic stem cell transplants (HSCT) utilize mobilized HSCs from peripheral blood. Granulocyte colony-stimulating factor (G-CSF) is the current standard of care for mobilization. G-CSF requires 4-7 days of injections and the number of CD34⁺ HSCs mobilized can be variable. G-CSF use is also associated with significant side effects including bone pain, nausea, headaches, fatigue, splenic rupture, and can have harmful effects in patients with both autoimmune and sickle cell disease. MGTA-145 is biologic agent (GROβT) that activates the CXCR2 pathway in neutrophils. When used in combination with plerixafor, a CXCR4 inhibitor, MGTA-145 has the potential to rapidly and reliably mobilize adequate numbers of HSCs for a successful transplant (≥2x10^6 CD34⁺/kg; Keever-Taylor *et al*, *BMT.* 2001) with a single dose and single same-day apheresis without the use of G-CSF. MGTA-145 plus plerixafor has been shown to rapidly mobilize HSCs in both mice and non-human primates within minutes and hours, respectively (Hoggatt *et al*, *Cell.* 2018; Goncalves *et al*, *Blood.* 2018). Based on these very encouraging preclinical data, Magenta initiated a Phase 1 study to evaluate the safety and efficacy of MGTA-145 as a single agent and in combination with plerixafor.

OBJECTIVES

- To assess the safety and tolerability of MGTA-145 as a single agent and in combination with plerixafor
- To investigate the pharmacokinetics and pharmacodynamics of MGTA-145 as a single agent and in combination with plerixafor
- To assess CD34⁺ and CD34⁺ CD90⁺ HSC mobilization after MGTA-145 as a single agent and in combination with plerixafor
- To assess the number of CD34⁺ HSCs mobilized and collected during apheresis

METHODS

- This study consists of four parts. In Part A, healthy volunteers were dosed with MGTA-145 (0.0075 – 0.3 mg/kg IV) or placebo. In Part B, subjects received a single dose of MGTA-145 (0.03 – 0.15 mg/kg IV) or placebo in combination with a single dose of plerixafor (0.24 mg/kg SC). In Part C, subjects received MGTA-145 or placebo plus plerixafor administered on day 1 and day 2. Part D is ongoing - subjects will receive a single dose of MGTA-145 (0.03 mg/kg IV) plus plerixafor followed by a single apheresis.
- Endpoints include safety and tolerability, pharmacokinetics, target engagement, and pharmacodynamic (PD) effects.
- PD was assessed by flow cytometry for peripheral blood CD34⁺ cell counts and cell surface neutrophil activation markers. ELISA assays were used for plasma concentration of neutrophil proteases including MMP-9 and its inhibitor TIMP-1.

MGTA-145-101 Healthy Volunteer Study Schema

Part A – Single Dose: MGTA-145
0.0075 - 0.3 mg/kg MGTA-145

Part B – Single Dose: MGTA-145 + plerixafor
0.03 - 0.15 mg/kg MGTA-145

Part C – 2 Daily Doses: MGTA-145 + plerixafor
0.03 and 0.07 mg/kg MGTA-145

Part D (Ongoing) **– Apheresis** MGTA-145 + plerixafor
0.03 mg/kg MGTA-145

RESULTS

Table 1: Subject Demographics

	Part A		Part B		Part C		Part D
	MGTA-145 n=24	Placebo n=12	MGTA-145 + plerixafor n=32	Plerixafor n=12	MGTA-145 + plerixafor n=8	Plerixafor n=2	MGTA-145 + plerixafor n=4*
Age, years (range)	43 (27 – 59)	40 (22 – 54)	39 (22 – 59)	37 (18 – 59)	35 (24 – 57)	35 (24 – 41)	40 (28-53)
Male (%)	20 (83)	8 (67)	33 (83)	9 (75)	8 (100)	1 (50)	3 (75)
Weight, kg (range)	85 (57 – 111)	83 (59 – 97)	80 (54 – 107)	78 (54 – 107)	77 (63 – 97)	77 (63 – 88)	84 (73-94)
Race, n White	14	5	15	5	4	1	2
Black/AA	7	6	24	6	4	1	2
Other	3	1	1	1	0	0	0

* Part D is ongoing.

Table 2: Treatment Emergent Adverse Events[1]

	Part A		Part B		Part C	
	MGTA-145 (0.0075 - 0.3 mg/kg)	Placebo	MGTA-145 + plerixafor (0.03 - 0.15 mg/kg)	Plerixafor	MGTA-145 + plerixafor (0.03 - 0.07)	Plerixafor
	n=24 n (%)	n=12 n (%)	n=32 n (%)	n=12 n (%)	n=8 n (%)	n=2 n (%)
Subjects with any drug related TEAE	**19 (79.2)**	**-**	**26 (81.3)**	**7 (58.3)**	**6 (75.0)**	**-**
Diarrhea	-	-	5 (15.6)	5 (41.7)	1 (12.5)	-
Nausea	-	-	5 (15.6)	2 (16.7)	1 (12.5)	-
Abdominal discomfort/pain	-	-	4 (12.5)	4 (33.3)	-	-
Vomiting	-	-	3 (9.4)	1 (8.3)	-	-
Back pain / Musculoskeletal pain[2]	19 (79.2)	-	20 (62.5)	1 (8.3)	4 (50.0)	-
Dizziness	-	-	5 (15.6)	1 (8.3)	-	-
Headache	-	-	3 (9.4)	1 (8.3)	1 (12.5)	-
Dysgeusia	-	-	-	2 (16.7)	-	-
Paraesthesia	-	-	2 (6.3)	-	1 (12.5)	-

[1] All AEs were grade 1 except for grade 2 abdominal pain (1), nausea (1), and back pain (1) in the plerixafor + MGTA-145 0.075 mg/kg 2h stagger cohort. There was no dose response in AEs, so data are aggregated.
[2] Back pain was associated with MGTA-145 infusion, lasted <20 minutes in most cases and did not require medical therapy.

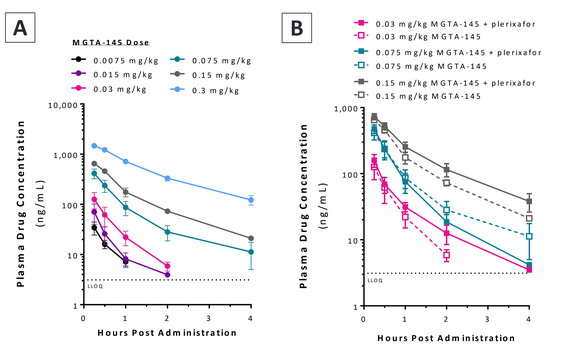


Figure 1: Pharmacokinetics of MGTA-145 Alone and in Combination with Plerixafor.
(A) Plasma concentrations of MGTA-145 following single dose administration (0.0075 - 0.3 mg/kg) as monotherapy in healthy subjects. **(B)** Plasma concentrations of MGTA-145 following single dose administration (0.03 - 0.15 mg/kg) in combination with a single dose of plerixafor (0.24 mg/kg) in healthy subjects. Data represent at least 4 subjects per dose level and are expressed as mean ± SEM.

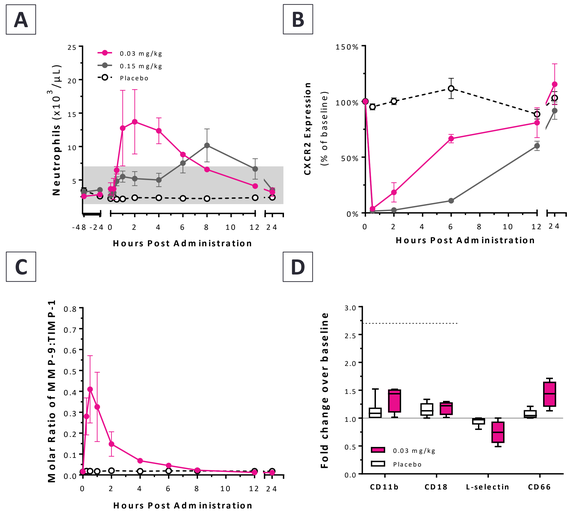


Figure 2: Confirmed Target Biology of MGTA-145 Monotherapy in Healthy Subjects.
(A) A single dose of MGTA-145 elicits dose-dependent mobilization of neutrophils into peripheral blood. **(B)** MGTA-145 monotherapy leads to rapid downregulation of its target receptor, CXCR2, on peripheral blood neutrophils. **(C)** MGTA-145 monotherapy leads to an increase in the molar ratio of the neutrophil protease, MMP-9, to its inhibitor, TIMP-1, in plasma. **(D)** MGTA-145 monotherapy elicits only modest changes in peripheral blood neutrophil activation markers (median ≤ 2-fold) after administration. Data represent at least 4 subjects per dose level and are expressed as mean ± SEM (A-C) or median + 10-90 percentile range (D). The shaded region in (A) represents the normal reference range for healthy subjects. The dotted line in (D) represents the anticipated effect of 5 days of G-CSF based on published data (Falanga *et al*, *Blood*. 1999).

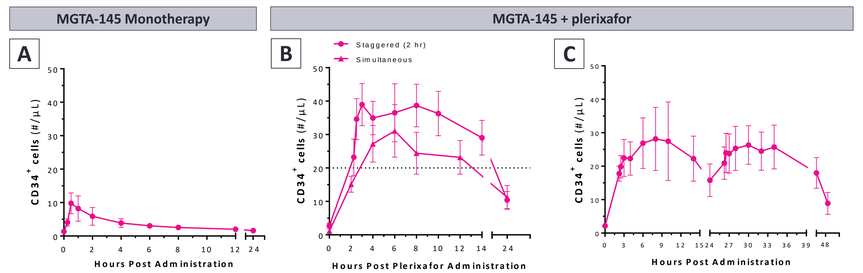


Figure 3: MGTA-145 Demonstrates Single Agent Activity and Leads to Robust Mobilization of CD34⁺ Cells in Healthy Subjects in Combination with Plerixafor.
A single injection of MGTA-145 (0.03 mg/kg) led to rapid mobilization of CD34⁺ cells. **(B)** When administered simultaneously or 2h after a single injection of plerixafor, MGTA-145 leads to robust mobilization of CD34⁺ cells. **(C)** Subjects in Part C received MGTA-145 2h after plerixafor and demonstrated reliable mobilization of CD34⁺ cells on Day 2 with peak counts that were comparable to Day 1 yields. Data represent at least 4 subjects per dose level and are expressed as mean ± SEM. Peak CD34+ counts for subjects that received plerixafor alone were comparable to previously reported yields (Chen *et al*, *Blood Advances*. 2018).

Table 3: Summary of One Day Mobilization Data

Mobilization Regimen	MGTA-145 dose (mg/kg)	Timing	% ≥ 20 / µL	% ≥ 40 / µL	Peak CD34⁺ (#/µL) Median (range)
MGTA-145 + plerixafor	0.03	Staggered (2h)	**83%** (5/6)	**50%** (3/6)	**40** (18-63)
		Simultaneous	**100%** (6/6)	**17%** (1/6)	**24** (20-70)
Plerixafor	0		**58%** (7/12)	**17%** (2/12)	**24** (13-78)

Table 4: Single-Day Mobilization and Apheresis Cell Yields

Subject	Total CD34⁺ Yield (x10^6 cells)	Body weight (kg)	CD34⁺/kg (x10^6 cells)	CD90⁺ (%)[b]
801	319	78.3	4.1	39%
807	322	72.6	4.4	41%
817	500	94.2	5.3	26%
821[a]	239	89.6	2.7	19%
Median	**321**	-	**4.3**	**33%**
		Clinical threshold for transplant:	**≥ 2.0**	

[a] Subject 821 completed 13L (65%) of the planned 20L apheresis; [b] CD90⁺ (%) represents the percentage of collected CD34⁺ cells that were CD90⁺ CD45RA⁻ based on internal data (n=2).

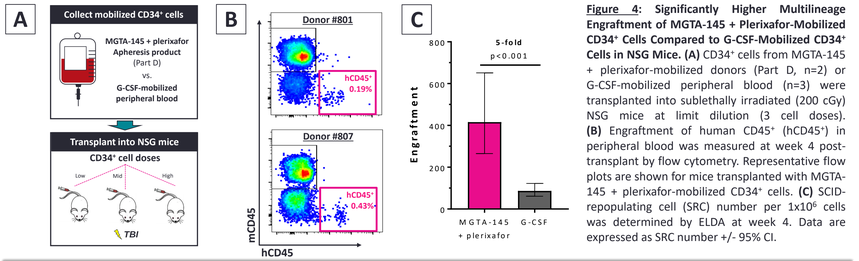
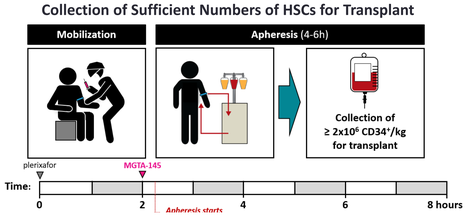


Figure 4: Significantly Higher Multilineage Engraftment of MGTA-145 + Plerixafor-Mobilized CD34⁺ Cells Compared to G-CSF-Mobilized CD34⁺ Cells in NSG Mice. (A) CD34⁺ cells from MGTA-145 + plerixafor-mobilized donors (Part D, n=2) or G-CSF-mobilized peripheral blood (n=3) were transplanted into sublethally irradiated (200 cGy) NSG mice at limit dilution (3 cell doses). **(B)** Engraftment of human CD45⁺ (hCD45⁺) in peripheral blood was measured at week 4 post-transplant by flow cytometry. Representative flow plots are shown for mice transplanted with MGTA-145 + plerixafor-mobilized CD34⁺ cells. **(C)** SCID-repopulating cell (SRC) number per 1x10^6 cells was determined by ELDA at week 4. Data are expressed as SRC number +/- 95% CI.

SUMMARY

- **MGTA-145 was well-tolerated in 69 subjects as monotherapy and in combination with plerixafor.**
- **MGTA-145 pharmacokinetics increases with dose proportionality that is not affected by plerixafor.**
- **MGTA-145 engages CXCR2 on neutrophils to mobilize CD34⁺ cells into peripheral blood with limited neutrophil activation.**
- **MGTA-145 in combination with plerixafor reliably mobilizes sufficient HSCs (median: 4.3x10^6 CD34⁺/kg) for a transplant.**
- **After dosing and apheresis, preliminary data suggest that MGTA-145 + plerixafor mobilizes HSCs enriched in engraftable CD34⁺ CD90⁺ cells.**

MGTA-145 + Plerixafor Enables Safe, Same-Day Mobilization & Collection of Sufficient Numbers of HSCs for Transplant



CONCLUSIONS

- **MGTA-145 administration is safe, as monotherapy or in combination with plerixafor, and leads to an additive increase in CD34⁺ cell mobilization.**
- **The number of high-quality cells mobilized by MGTA-145 + plerixafor provides a strong rationale for conducting mobilization studies of allogeneic and autologous transplant in autoimmune diseases, hematopoietic gene therapy and hematologic malignancies.**
- **Additional studies to fully characterize MGTA-145 + plerixafor apheresis products, including preclinical engraftment and graft versus host disease (GvHD) studies in mice, are ongoing.**

	G-CSF	MGTA-145 + plerixafor
Mechanism of action	Bone remodeling	Chemokine cell migration
Time to mobilize and collect	5+ days	<1 day
Tolerability	Majority with bone pain, headache, myalgia, and/or fatigue (up to 1+ week)[a]	Majority with transient, grade 1 back pain (most <20 minutes)
Efficacy (≥2x10^6 CD34⁺/kg)	78%[b]	100% (4/4)
Quality of CD34⁺ (% CD90⁺)	10%	33%
Function of CD34⁺	-	5x increased engraftment in mice

[a] Pulsipher *et al*, *Blood*. 2009; [b] Holig, *Transfus Med Hemother.* 2013.