2 SYNOPSIS

Name of Sponsor/Company: MacroGenics, Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: Flotetuzumab (MGD006)	**Volume:**	
Name of Active Ingredient(s): CD123 x CD3 DART® bi-specific antibody-based molecule	**Page:**	

Study Number: CP-MGD006-01

Title of Study:

A Phase 1/2, First-in-Human, Dose Escalation Study of MGD006, a CD123 x CD3 Dual Affinity Re-Targeting (DART) Bi-Specific Antibody-Based Molecule, in Patients with Relapsed or Refractory Acute Myeloid Leukemia or Intermediate-2/High Risk Myelodysplastic Syndrome

Coordinating Principal Investigator:

MD, PhD, Washington University School of Medicine, St Louis, MO, USA.

Study Center(s):

This study was executed at 36 sites in 7 countries.

Publication (Reference):

Not required for an abbreviated report.

Study Period: 09-Jun-2014 (first patient dosed) 05-Jul-2022 (last patient end of study)	**Phase of development:** Phase 1/2

Objectives:

Objectives denoted by an asterisk (*) were not assessed, due to the sponsor's decision to terminate the study early and to not pursue further development of flotetuzumab.

Primary Objective

To assess the anti-neoplastic activity of flotetuzumab in patients with primary induction failure (PIF)/early relapse (ER) acute myeloid leukemia (AML), as determined by the proportion of patients who achieve complete remission (CR)/CR with partial hematologic recovery (CRh).

Secondary Objectives

- Assessment of CR rate, CRh rate, overall complete response rate (OCRR; CR, CRh, CR with incomplete blood cell recovery [CRi; CR with incomplete neutrophil recovery (CRn), CR with incomplete platelet recovery (CRp)], or morphologic leukemia free state [MLFS]), objective response rate (CR, CRh, CRi [CRn, CRp], MLFS, or partial remission [PR]), time to response and duration of response (DoR).
- To measure early mortality rates, overall survival (OS) and event-free survival (EFS).*
- To determine the rate of eligible patients, per institution criteria, that transition to successful stem cell transplant after achieving overall complete response (CR, CRh, CRi [CRn, CRp], or MLFS).
- To assess rate of conversion to and maintenance of transfusion independence.*
- To evaluate duration of initial hospitalization for flotetuzumab administration.*
- To evaluate incidence and duration of hospitalizations subsequent to initial discharge.*

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- To monitor the safety and tolerability of flotetuzumab.
- To characterize the pharmacokinetics (PK) and immunogenicity of flotetuzumab.
- To determine safety and efficacy of tocilizumab in the treatment of infusion related reactions (IRR)/cytokine release syndrome (CRS).*

Exploratory Objectives *

- To evaluate CD123 expression on blast cells.
- To evaluate circulating cytokine levels at baseline and over time.
- To evaluate circulating leukemic and normal cells at baseline and over time.
- To evaluate circulating T lymphocyte populations and activation markers at baseline and over time.
- To evaluate leukemic cells, leukemic stem cells, normal progenitor cells and T lymphocytes at baseline and over time in the bone marrow.
- To evaluate molecular markers of minimal residual disease (MRD).
- To examine changes in T lymphocyte repertoire.
- To evaluate the correlation between cytogenetic abnormalities with responses to flotetuzumab immunotherapy.
- To study adaptive immune changes during flotetuzumab treatment.
- To study the tumor microenvironment (TME) immune contexture.
- **Ruxolitinib Cohort Objectives:**
    - To characterize the onset, duration, and severity of IRR/CRS on an exploratory, pilot basis in flotetuzumab-treated patients receiving ruxolitinib and compare that to historical experience in patients not receiving ruxolitinib.
    - To measure and compare cytokine profile and T-lymphocyte populations in patients receiving the combination of ruxolitinib and flotetuzumab vs flotetuzumab alone.
    - To determine the safety and tolerability of the combination of ruxolitinib and flotetuzumab.

Methodology:

This was an open-label, multi-dose, single-arm, multi-center, Phase 1/2, dose-escalation and expansion study to define a maximum tolerated dose and schedule (MTDS), describe preliminarily safety, and to assess PK, immunogenicity, immunomodulatory activity, and potential anti-neoplastic activity of flotetuzumab in patients with AML and myelodysplastic syndrome (MDS) whose disease was not expected to benefit from cytotoxic chemotherapy.

This study was designed in three segments: 1) the Single Patient Dose Escalation Segment, 2) the Multi-Patient Dose Escalation Segment and MTDS, and 3) the Expansion Cohort segment. In all segments of the study, flotetuzumab was administered using a series of continuous intravenous (IV) infusions administered on a weekly basis.

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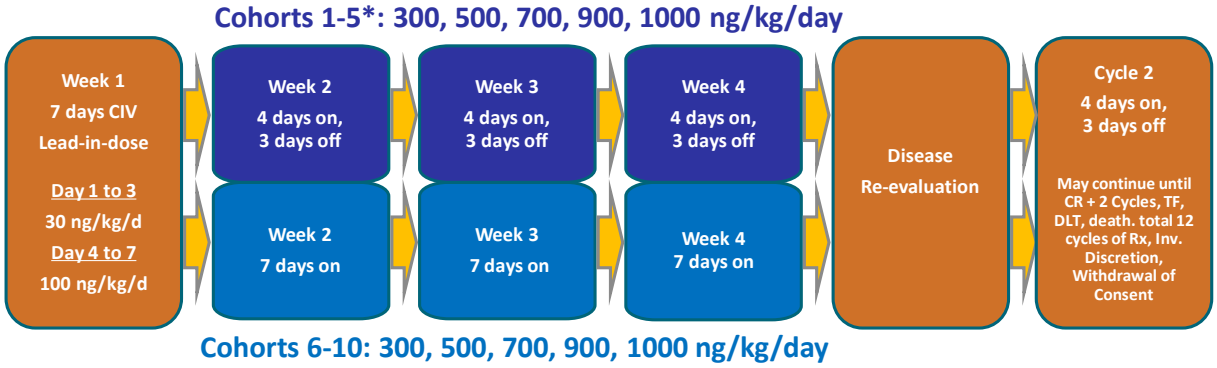
Single Patient Dose Escalation Segment

In the initial Single Patient Dose Escalation Segment, four 1-patient mini-cohorts (1+3 design; constituting, in aggregate, **Cohort 0**) were used to examine the effects of one 4-week cycle of very low doses of flotetuzumab, at doses of 3, 10, 30 and 100 ng/kg/day, administered on a 4 days on/3 days off schedule. This initial phase of the study was implemented to cautiously establish an acceptable starting dose for the second segment of the study, in view of the potential for systemic cytokine production with this T-cell activating molecule.

Multi-Patient Dose Escalation Segment

The Multi-Patient Dose Escalation Segment employed a classical 3 + 3 dose escalation study design in patients with either AML or MDS. Prior to Amendment 5, all patients in this segment were to be treated with 100 ng/kg/day for 4 days on/3 days off in Week 1, followed by a step-up dose (to 300, 500, 700, 900, or 1000 ng/kg/day in **Cohorts 1, 2, 3, 4, and 5**, respectively) for 4 days on/3 days off in Week 2 and beyond (**Figure 1**). This step-up dosing followed the Good Laboratory Practice (GLP) toxicology study in which intra-monkey dose escalation appeared to enhance tolerability of flotetuzumab, apparently through reduction in cytokine release. Starting with Amendment 5, two modifications to the dosing scheme were made. The first was to include an additional step-up dose (two-step lead-in dose: 30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days) during the first week of dosing to minimize the extent of IRR/CRS. The second was to evaluate, in parallel, a 7-day continuous infusion schedule in Weeks 2-4 during Cycle 1, to ameliorate IRR/CRS and AML circulating blast rebound noted with intermittent (4 days on/3 days off) dosing. The patients on the continuous infusion schedule were to receive the two-step lead-dose in Week 1, followed by 300, 500, 700, 900, and 1000 ng/kg/day in **Cohorts 6, 7, 8, 9, and 10**, respectively, in Week 2 and beyond.

Figure 1 **Study Design – Multi-Patient Dose Escalation Segment**



*** Cohorts 1 and 2 used a Week 1 lead-in-dose of 100 ng/kg/day for 4 days, followed by 3 days off, prior to the Week 2 step-up dose. Cohorts 2a-10 were to use the Week 1 schedule as shown in the figure.**
Abbreviations: CIV: continuous intravenous; CR: complete remission; d: day; DLT: dose limiting toxicity; Inv: investigator; Rx: treatment; TF: treatment failure.

As of 28-Jul-2017, by agreement of the sponsor's medical monitor, the sponsor's pharmacovigilance physician, the independent data safety monitor (DSM), and participating investigators, the maximum tolerated dose (MTD) in this study was established as 500 ng/kg/day across both dosing schedules. The 7-day on schedule was selected to open the Cohort Expansion phase of the study, because it was tolerated and potentially offered better anti-

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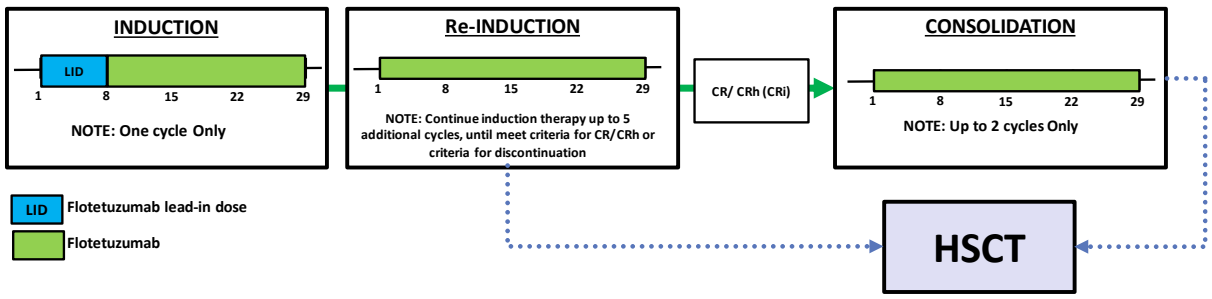
leukemic activity. The recommended MTDS was therefore defined as initial two-step lead-in dose on Week 1 followed by 500 ng/kg/day administered by continuous intravenous infusion.

Cohort Expansion Segment

As of Amendment 8, the lead-in dose was modified from a two-step lead-in dose to a multi-step lead-in dose, comprised of sequential smaller and more frequent dose increments (30 to 60 to 100 to 200 to 300 to 400 to 500 every 24 hours) until reaching the MTD of 500 ng/kg/day. Although more involved, it was anticipated that this more conservative approach to intrapatient dose escalation may further attenuate IRR/CRS.

Prior to Amendment 9, all patients eligible to receive flotetuzumab beyond Cycle 1 received drug on a 4 days on/3 days off schedule in Cycle 2 and beyond. With Amendment 9, dosing was modified to specify 2 treatment phases, "Induction" (up to six 28-day cycles of continuous IV infusion [with multi-step lead-in dosing during Week 1 of Cycle 1] until response criteria were met), followed by "Consolidation" (up to two 28-day cycles of 4 days on/3 days off each week). With Amendment 11 all cycles of flotetuzumab, whether induction or consolidation, were administered as a continuous infusion in 28-day cycles (see **Figure 2**).

Figure 2 **Induction and Consolidation Treatment in the Expansion Cohort**



Number of Patients (planned and analyzed):

Planned: approximately 283
Enrolled: 250
Safety Population: 244
Efficacy Population: 72 (51 PIF; 21 ER)

Diagnosis and Criteria for Inclusion:

The patient population enrolled in this study consisted of patients ≥ 18 years of age; with a confirmed diagnosis of relapsed or refractory primary or secondary AML (any subtype except acute promyelocytic leukemia) according to World Health Organization classification, or MDS* with an International Prognostic Scoring System (IPSS) risk category of Intermediate-2 or High Risk; and Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.

* As of Amendment 7, the sponsor stopped enrolling patients with MDS into this study for business reasons.

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Test Product, Dose, Mode of Administration, and Batch Number:

Drug: Flotetuzumab.

Dose:

- Dose escalation:
  - 3, 10, 30, or 100 ng/kg/day with no lead-in dose.
  - 300, 500, or 700 ng/kg/day with lead-in dose during Week 1 (depending on cohort number: 100 ng/kg/day; or 30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days).
- Cohort expansion: 500 mg/kg/day with lead-in dose during Week 1 (30 ng/kg/day for 3 days followed by 100 ng/kg/day for 4 days; or 30 to 60 to 100 to 200 to 300 to 400 to 500 every 24 hours).

Mode of Administration: Continuous weekly IV infusion on 4-day on/3-day off or 7-day on schedule, depending on cohort and week or cycle number.

Batch Number(s):

- Flotetuzumab: 1-FIN-1884, 1-FIN-2639, 1-FIN-3052, 3-FIN-3111, 3-FIN-3289
- MGV001 Vehicle: 3-FIN-1941, 3-FIN-2119, 3-FIN-2176
- MGV004 IV Solution Stabilizer: 3-FIN-2931, 3-FIN-3226, 3-FIN-3228

Reference Product, Dose, Mode of Administration, and Batch Number:

None

Duration of Treatment:

Patients in each segment of the study were treated for the number of cycles indicated below or until protocol-specified discontinuation criteria were met.

Single Patient Dose Escalation Segment

One four-week treatment cycle.

Multi-Patient Dose Escalation Segment

Up to 12 four-week treatment cycles.

Cohort Expansion Segment

Up to 8 four-week treatment cycles (maximum of 6 induction plus maximum of 2 consolidation).

Under Amendments 7 through 10, patients who relapsed after achieving a complete response (CRx), CRi, or MLFS could be retreated with flotetuzumab.

Under Amendments 11 through 13, patients who completed treatment and were scheduled for a stem cell transplant could continue to receive flotetuzumab treatment until the time of the transplant.

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Criteria for Evaluation:

Efficacy Assessments

Evidence of clinical activity was assessed by the study investigators by using complete blood count (CBC) and peripheral blood cell morphological examination, examination of bone marrow aspiration (or biopsy if required), and physical exam according to the rules modified from the Revised Recommendations of the International Working Group (IWG) for Diagnosis Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Response assessment was based on bone marrow aspirate/biopsy and the best CBC up to 14 days post bone marrow aspirate/biopsy. Responses were categorized as:

- CR: mCR (morphologic CR), CRc (cytogenic CR), or CRm (molecular CR);
- CRh (CR with partial hematologic recovery);
- CRi (CR with incomplete blood count recovery): CRn (CR with incomplete neutrophil recovery) or CRp (CR with incomplete platelet recovery);
- MLFS (morphologic leukemia free state);
- PR (partial response);
- OB (other benefit);
- SD (stable disease);
- PD (progressive disease).

Pharmacokinetic and Immunogenicity Assessments

A validated assay was used to measure flotetuzumab concentrations in human serum. Flotetuzumab PK were characterized across doses ranging from 3 to 500 ng/kg/day.

Anti-drug antibodies (ADA) to flotetuzumab were measured at a sponsor-designated central laboratory using a validated bridging enzyme-linked immunosorbent assay (ELISA).

Safety Assessments

The safety assessment was based on adverse events (AEs) that occurred from first administration of study drug until 28 days after the last dose of study drug or until the start of another systemic anticancer therapy, if earlier. Events related to leukemia progression/worsening of underlying disease (including those with a fatal outcome) were to be collected as efficacy endpoints, and not documented as AEs/serious AEs (SAEs). Clinically significant abnormal laboratory, vital sign, and electrocardiogram (ECG) findings were reported as AEs.

Statistical Methods:

Analysis Populations

- **Efficacy population** – All patients that enrolled under Protocol Amendment 11 or later and treated with flotetuzumab at the MTD of 500 ng/kg/day as a continuous 7-day per week IV infusion during Cycle 1, had received any portion of one dose of flotetuzumab, and met the definition of PIF/ER AML based on inclusion criteria as revised in Amendment 11).

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- **Safety population** – All patients who received any portion of any dose of flotetuzumab.

Analysis Methods

Summary statistics consisted of absolute and relative frequencies of each category of discrete variables as well as of means, standard deviations, medians, minimum and maximum values of continuous variables.

The primary efficacy endpoint for the AML expansion cohort was the CR/CRh rate, calculated as the proportion of patients in the efficacy population that achieved a best response of CR (mCR, CRc, or CRm) or CRh at any point during treatment by investigator's assessment, according to IWG AML response criteria.

DoR was calculated from the time of initial documentation of response to the time of disease relapse or death due to any cause, whichever occurred first. Patients who were still in response at study completion without alternative therapies were censored at the time of their last disease assessment.

Adverse events were summarized by System Organ Class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA 25.0), by severity using common terminology criteria for adverse events (CTCAE v4.0), and by relationship to study therapy using investigator assessment. Patients were counted only once for each PT, once for each SOC, and by the highest event severity, regardless of how many events that patient experienced.

Summary of Results:

Patient Disposition

Enrollment in the study was terminated early by the sponsor, during the Cohort Expansion segment, due to the sponsor's decision against pursuing further development of flotetuzumab. The decision to terminate enrollment was not due to safety concerns.

Of 374 patients screened, 250 were enrolled in 7 countries and 244 received study treatment. Of the 244 patients treated, 5 (2.0%) completed treatment per protocol. The most common reason for discontinuation of treatment was progressive disease (88, 35.2%). The most common reason for discontinuation of study was death (192, 76.8%).

Demography

The mean age was 59.5 years. The majority of patients were male (135, 55.3%), white (183, 75.0%), not Hispanic or Latino (200, 82.0%), and had an ECOG status of 1 (165, 67.6%). Most patients (236, 96.7%) had AML, while 8 (3.3%) had MDS.

Efficacy Results

Flotetuzumab demonstrated anti-leukemic activity in patients with PIF or ER. In the safety population 17 (7.0%) patients had a best overall response (BOR) of CR and 22 (9.0%) patients had a BOR of either CR or CRh; mean (standard deviation [SD]) DoR was 1.5 (1.22) months. In the efficacy population 9 (12.5%) patients had a BOR of CR (8/51, 15.7% PIF; 1/21, 4.8% ER) and no patients had a BOR of CRh; mean (SD) DoR was 1.2 (1.16) months.

In the safety population 11 (4.5%) of 244 patients had HSCT. In the efficacy population 3 (4.2%) of 72 patients had HSCT (2/51, 3.9% PIF; 1/21, 4.8% ER).

Pharmacokinetics

Flotetuzumab PK was generally linear across the dose range evaluated. High interpatient variability was observed in flotetuzumab PK. Preliminary analysis of flotetuzumab serum concentration indicated flotetuzumab PK was best fit by a two compartment PK model. In addition, flotetuzumab demonstrated a high clearance rate and a short half-life. Flotetuzumab volume of distribution at steady-state suggests high tissue distribution and/or binding. Exposure-response and exposure-safety analyses demonstrated that a dose of 500 ng/kg/day flotetuzumab administered as continuous infusions provided optimal benefit-risk ratio in patients with relapsed/refractory AML.

Immunogenicity

ADA induction by flotetuzumab was minimal (1.0%).

Safety Results

Overall, flotetuzumab at the MTD of 500 ng/kg/day demonstrated an acceptable safety profile in patients with AML and MDS whose disease was not expected to benefit from cytotoxic chemotherapy.

- The dose level of 700 ng/kg/day flotetuzumab across both dosing schedules (4-day on/3-day off and 7-day on) was deemed to have exceeded the MTD, as a result of IRR dose limiting toxicities (DLTs). The MTD across both dosing schedules was determined to be 500 ng/kg/day.
- The most common AEs across all cohorts (≥ 40% of patients) were IRR (125, 51.2%), CRS (112, 45.9%), diarrhea (104, 42.6%), peripheral edema (102, 41.8%), hypokalemia (101, 41.4), and nausea (98, 40.2%).
- The most common treatment-related AEs across all cohorts (≥ 20% of patients) were IRR (125, 51.2%), CRS (112, 45.9%), peripheral edema (51, 20.9%), and nausea (49, 20.1%).
- Treatment-related AEs of Grade ≥ 3 were experienced by 135 (55.3%) patients across all cohorts. By maximum severity grade, 96 (39.3%) patients had Grade 3 events, 34 (13.9%) had Grade 4 events, and 5 (2.0%) had Grade 5 events.
- The majority of Grade 4 treatment-related events were AML-associated hematologic events. Five patients experienced fatal (Grade 5) treatment-related events, which were cardiac arrest, sepsis, infectious enterocolitis, lactic acidosis, and hypercapnic coma (1 patient, 0.4% each).
- 65 (26.6%) patients across all cohorts experienced at least 1 treatment-related SAE. The most common treatment-related SAEs (≥ 10 patients) were CRS (13, 5.3%) and IRR (10, 4.1% each).
- 46 (18.9%) patients across all cohorts discontinued study treatment due to an AE. The most common (≥ 1% of patients) AEs leading to treatment discontinuation were IRR (12, 4.9%) and respiratory failure (4, 1.6%).
- 227 (93.0%) patients across all cohorts had at least 1 AE leading to study treatment interruption or modification, most commonly (≥ 5% of patients) IRR (117, 48.0%), CRS (103, 42.4%), and pyrexia (19, 7.8%).
- 220 (90.2%) patients across all cohorts experienced at least 1 event of IRR/CRS reported as an AESI. IRR/CRS symptoms typically included tachycardia, hypotension, pyrexia, chills, and/or respiratory symptoms.
    - IRR/CRS events were manageable with treatment interruption, dose reduction, early use of tocilizumab, and medical intervention with antipyretics, antihistamines, and corticosteroids. Notably, multistep lead-in dosing was associated with a reduced frequency and/or severity of IRR/CRS. A majority of IRR/CRS events were of short duration (24 to 48 hours) and reversible with no clinical sequelae.
- No specific safety signal for flotetuzumab was identified based on review of laboratory, vital sign, and cardiac function AEs.

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Conclusion:

- Overall, flotetuzumab at 500 ng/kg/day demonstrated an acceptable safety profile in patients with AML and MDS whose disease was not expected to benefit from cytotoxic chemotherapy.
    - The safety profile of flotetuzumab showed no unexpected safety findings, with safety observations consistent with the mechanism of action of flotetuzumab (IRR/CSR) or with the patient's underlying disease.
- Flotetuzumab demonstrated anti-leukemic activity in patients with PIF or ER:
    - In the efficacy population 9 (12.5%) of 72 patients had a BOR of CR (8/51, 15.7% PIF; 1/21, 4.8% ER) and no patients had a BOR of CRh.
    - In the efficacy population 3 (4.2%) of 72 patients had HSCT (2/51, 3.9% PIF; 1/21, 4.8% ER).
- Flotetuzumab PK was generally linear across the dose range evaluated. High interpatient variability was observed in flotetuzumab PK. Preliminary analysis of flotetuzumab serum concentration indicated flotetuzumab PK was best fit by a two compartment PK model. In addition, flotetuzumab demonstrated a high clearance rate and a short half-life. Flotetuzumab volume of distribution at steady-state suggests high tissue distribution and/or binding.
- Exposure-response and exposure-safety analyses demonstrated that a dose of 500 ng/kg/day flotetuzumab administered as continuous infusions provided optimal benefit-risk ratio in patients with relapsed/refractory AML.
- ADA induction by flotetuzumab was minimal (1.0%).

Date of the Report: 17 March 2023