INTRODUCTION
GBR 1342 is a novel CD3xCD38 bispecific antibody engineered (using the Glenmark Bispecific Engagement by Antibodies based on the T-cell receptor [BEAT]® platform) to direct T-cells to CD38-expressing myeloma cells by engaging the CD3 molecule on T lymphocytes and the CD38 antigen on tumor cells, thereby killing the bound target cells through redirected lysis (Figure 1).

- Includes a single chain, variable fragment arm with anti-CD38 specificity and a fragment antigen binding (Fab) arm with anti-CD3 specificity.
- Has full antibody-like pharmacokinetics with a long elimination half-life of approximately 110 hours (in rats), which is similar to IgG and therefore permits intermittent dosing.
- Has low immunogenicity potential.
- Fcy receptor binding is engineered to reduce complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) effector functions.

Figure 1. GBR 1342 BEAT® Design and Redirected Lysis

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Figure 2. GBR 1342 BEAT® Design and Redirected Lysis

STUDY STATUS
The first clinical study of GBR 1342 (GBR 1342-101, NCT03309111) is currently recruiting and enrolling patients in the United States.

STUDY OBJECTIVES
This two-part, first-in-human clinical study of GBR 1342 aims to:
1. Evaluate the safety profile and maximum tolerated dose (MTD) of GBR 1342 monotherapy in subjects with relapsed/refractory multiple myeloma.
2. Further elucidate the safety, tolerability, and preliminary clinical activity (objective response, pharmacokinetics [PK], immunogenicity) of GBR 1342 at the MTD.

STUDY DESIGN
Phase I multicenter, open-label, two-part, dose-escalation study of GBR 1342 monotherapy in subjects with previously treated multiple myeloma.

The study is being conducted in compliance with Good Clinical Practice. The protocol and informed consent were approved by local institutional review boards and written informed consent was obtained from all subjects prior to entry into the study.

Part 1: Dose-Finding Study
- Currently enrolling approximately 60 adult subjects with multiple myeloma who have received prior therapies.

Part 2: Expansion Study
- Plans to enroll an additional 65 subjects with multiple myeloma who have received prior therapies.
- Subjects will be treated at the MTD identified in Part 1 to further evaluate the safety, PK, and preliminary anti-tumor activity of GBR 1342 until disease progression or unacceptable toxicity occurs.

STUDY SUBJECTS (PART 1)
Key Inclusion Criteria:
- Adults ≥18 years with no prior therapeutic options of known or proven benefit, in the opinion of the investigator.
- Measurable disease, defined as any quantifiable mononuclear protein value by % of the following measures:
  - Serum M protein ≥10 g/L (for IgG 25 g/L), or
  - Urine light-chain (M protein) ≥200 mg/24 hours, or
  - Serum free light chain (FLC) assay: involved free light chain (FLC) level ≥10 mg/dL provided FLC ratio is abnormal
- Eastern Cooperative Oncology Group (ECOG) performance-status score of ≤2
- Absolute neutrophil count ≥1500/mm3 and platelet count ≥200×10^9/L, and hemoglobin ≥75 g/dL (unless decreases are caused by myeloma, defined by bone marrow infiltration of ≥50%)
- Serum creatinine ≤2× upper limit of normal (ULN) or creatinine clearance ≥20 mL/minute/1.73 m²
- Serum albumin ≥3.5 g/dL
- Bilirubin ≤2.5× ULN
- Known allergy to any of the ingredients in the formulation (i.e., citrate, sucrose, Tween) or known allergy for which the minimum washout period should be 8 weeks
- Known allergy to any related class of compounds

Exclusion Criteria:
- Intensive or inpatient care required for organ dysfunction.
- Active infection requiring hospitalization or intensive care in the past 4 weeks.
- Use of any investigational drug within 4 weeks of the start of study drug or concomitantly with study drug.
- Subjects not recovered to at least Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 for all previously treated toxicities.
- Subjects with any of the following according to the MTD:
  - Serum creatinine ≥2× upper limit of normal (ULN) or creatinine clearance <20 mL/minute/1.73 m²
  - Serum albumin <3.5 g/dL
  - Bilirubin ≥2.5× ULN
  - Known allergy to any ingredient in the formulation
  - Known allergy for which the minimum washout period should be 8 weeks
  - Known allergy to any related class of compounds

Dose Escalation Scheme
- Cohort design: 3+3 design
- Dose escalation: 2× weekly until disease progression or unacceptable toxicity occurs
- Dose-limiting toxicity (DLT) is defined as:
  - Any grade 3 or 4 toxicities, except for the following:
    - Alopecia
    - Pruritus

Table 1. GBR 1342 Dose Escalation Scheme

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
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</tr>
<tr>
<td>Day 15</td>
<td>60</td>
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<td>Day 1</td>
<td>500</td>
</tr>
<tr>
<td>Day 15</td>
<td>1000</td>
</tr>
</tbody>
</table>

Determination of Maximum Tolerable Dose (MTD)
- Dose escalation follows a modified 3+3 design initially with 4 single subject cohorts (Cohorts 1-4) and switches to a classical 3+3 design with intra-subject dose escalation (Figure 4).

- Adverse events (AEs) constitute a dose limiting toxicity (DLT) if one of the following conditions applies:
  - Non-hematologic toxicity CTCAE Grade ≥3, except for:
    - Alopecia of any CTCAE grade
    - Any other CTCAE Grade ≥3 skin toxicity recovered to Grade ≤1 within 2 weeks after last dose
    - CTCAE Grade 3 fatigue recovered to Grade ≤2 within 2 weeks after last dose
    - CTCAE Grade 3 hematologic toxicity CTCAE Grade 3 hematologic anemia, CTCAE Grade 4 anemia, CTCAE Grade 4 neutropenia lasting 7 days, CTCAE Grade 3 or 4 for fibrosis, CTCAE Grade 3 thromocytopenia lasting more than 7 days
    - Any other AE that in the opinion of the Data Safety Monitoring Committee constitutes a safety threat to the subject

- The observation period for DLT is the 28 days following the first administration of study drug.

- Subjects will receive GBR 1342 treatment until either disease progression or unacceptable toxicity occurs.

STUDY ENDPOINTS
Primary endpoints:
- Frequency and severity of AEs
- Number of DLTs during the first 28 days after the first administration of study drug

Secondary endpoints:
- Objective response to GBR 1342 according to International Myeloma Working Group (IMWG) response criteria
- Pharmacokinetics (PK), immunogenicity (of GBR 1342 at the MTD)
- Switches to a classical 3+3 design with intra-subject dose escalation (Figure 4)

- Any other CTCAE Grade ≥3 skin toxicity recovered to Grade ≤1 within 2 weeks after last dose
- CTCAE Grade 3 fatigue recovered to Grade ≤2 within 2 weeks after last dose
- CTCAE Grade 3 hematologic toxicity CTCAE Grade 3 hematologic anemia, CTCAE Grade 4 anemia, CTCAE Grade 4 neutropenia lasting 7 days, CTCAE Grade 3 or 4 for fibrosis, CTCAE Grade 3 thromocytopenia lasting more than 7 days
- Any other AE that in the opinion of the Data Safety Monitoring Committee constitutes a safety threat to the subject

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REFERENCES