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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Sabatolimab (MBG453), nisevokitug (NIS793) and canakinumab (ACZ885)

Trial Indication(s)

Lower risk (very low, low, or intermediate risk) myelodysplastic syndrome (MDS)

Protocol Number

CMBG453E12101

Protocol Title

A Phase Ib, multicenter, open-label platform study of select drug combinations in adult patients with lower risk (very low, low, or intermediate risk) myelodysplastic syndrome

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 3 (MBG453 and NIS793) and Phase 4 (canakinumab)

Study Start/End Dates

Study Start Date: June 18, 2021 (Actual)

Primary Completion Date: April 19, 2024 (Actual)
Study Completion Date: April 19, 2024 (Actual)

Reason for Termination (If applicable)

On 22-Sep-2023, Novartis decided that none of the treatment arms would enroll any new participants due to a business decision and that the study would not progress into the expansion phase in any of the arms. The two participants who remained on-treatment in Arm 1 at that time of this decision continued to receive treatment according to the latest protocol version approved.

The last patient on study discontinued safety follow up on 19-Apr-2024. Therefore, 19- Apr-2024 is considered the global LPLV date for this study. Given that the study did not fully enroll the initial target number of participants described in the protocol, in jurisdictions where applicable, this global LPLV date is also considered the early termination date of the study.

Study Design/Methodology

This was a phase Ib, multi-arm, open-label platform study in which investigational drugs were evaluated individually as single agents and in combinations. The study was comprised of a dose escalation/confirmation part and a dose expansion part.

In total, 33 participants were treated in the dose confirmation/escalation part of the study across the 5 treatment arms as follows:

- Arm 1: 17 participants treated with MBG453 800 mg once every 4 weeks (Q4W) (dose confirmation)
- Arm 2: 8 participants treated with NIS793 1400 mg once every 3 weeks Q3W (dose escalation)
- Arm 3: 6 participants treated with canakinumab 250 mg Q4W (dose confirmation)
- Arm 4: No participants treated with MBG453 600 mg Q4W + NIS793 1400 mg Q3W
- Arm 5: 2 participants treated with MBG453 800 mg Q4W + canakinumab 250 mg Q4W

The study did not progress into the expansion phase in any of the arms.

Centers

13 centers in 7 countries: Singapore(2), Australia(1), Spain(2), Israel(1), Korea, Republic of(1), United States(5), Italy(1)

Objectives:

The primary objective of the trial was to characterize the safety, tolerability and confirm dose for single agents and combinations.

The secondary objectives were:

- To evaluate the efficacy of single agents and combinations on transfusion burden and hematologic parameters in participants who are transfusion dependent
- To evaluate the efficacy of single agents and combinations on hematologic parameters in participants who are transfusion independent
- To characterize the pharmacokinetics (PK) of single agents and combinations
- To characterize the prevalence and incidence of immunogenicity of single agents and combinations

Test Product (s), Dose(s), and Mode(s) of Administration

Treatments

For this study, the terms “investigational drug” or “study drug” referred to MBG453 (sabatolimab), NIS793, (nisevokitug) and canakinumab (ACZ885). “Study treatment” referred to a specific single agent or combination treatment.

MBG453, NIS793, and canakinumab were administered as single agents or in combination (MBG453 + canakinumab).

MBG453 was administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W).

Canakinumab was administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W.

NIS793 was administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W).

The treatment period started on Cycle 1 Day 1 and each treatment cycle had a duration of 28 days (Q4W schedule) or 21 days (Q3W schedule).

Participants were planned to be treated for a minimum of six months (approximately 7 cycles of treatment for 28-day cycles and 9 cycles of treatment for 21-day cycles) unless they experienced unacceptable toxicity, progressive disease, and/or treatment was discontinued at the discretion of the investigator or the patient.

Statistical Methods

The Full Analysis Set (FAS) and safety set comprised all participants who received at least one dose of study treatment (i.e., at least one dose of any component of the combination therapy). The dose determining set included all FAS participants in dose escalation/confirmation and expansion parts who met the minimum exposure criterion (received all planned doses within the first 56 days of dosing) and had sufficient safety evaluations (as determined by Novartis and investigator) or experienced a dose-limiting toxicity (DLT) during the DLT evaluation period. The pharmacokinetic analysis set included all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study treatment and with no protocol deviations that impact on PK data. The immunogenicity (IG) prevalence set included all participants in the FAS with a determinant baseline IG sample or at least one determinant post-baseline IG sample. The immunogenicity prevalence set was defined separately for MBG453, NIS793 and canakinumab. The immunogenicity incidence set included all participants in the immunogenicity prevalence set with a non-missing baseline IG sample and at least one non-missing post-baseline IG sample.

The Kaplan-Meier (KM) analysis for secondary efficacy endpoints were only conducted if there were at least 10 participants treated in the same treatment arm.

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Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Participants must be ≥ 18 years of age at the time of signing the informed consent form (ICF).
3. Participants must have a diagnosis prior to participation in the study of IPSS-R very low, low, or intermediate risk MDS with ≤10% bone marrow blasts and one or more of the following:

a. Symptomatic anemia with hemoglobin <10 g/dL that has relapsed after or is refractory to ESAs (or the patient is intolerant to ESAs)

b. Symptomatic anemia with hemoglobin <10 g/dL) that is ESA-naive with EPO level ≥ 500 /uL

c. Thrombocytopenia with platelets <30,000/uL or with clinically significant bleeding or bruising and platelets <50,000/uL

d. Neutropenia with an absolute neutrophil count (ANC) <500/ µL or with recurrent and/or severe infections and an ANC that is <1000/ µL and amenable to response assessments by International Working Group (IWG) response criteria in myelodysplasia (Cheson et al 2006)

4. Participants who are refractory to, intolerant of, or ineligible/unable to receive SOC therapeutic options including lenalidomide
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2
6. Patient must be a candidate for serial bone marrow aspirate and/or biopsy according to the institutions' guidelines and be willing to undergo a bone marrow aspirate and/or biopsy at screening, during and at the end of therapy on this study

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Key Exclusion Criteria:

1. Systemic antineoplastic therapy (including cytotoxic chemotherapy, alpha-interferon, kinase inhibitors or other targeted

small molecules, and toxin-immunoconjugates) or any experimental therapy within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment.

2. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

3. Participants with chronic myelomonocytic leukemia (CMML) or myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

4. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or ESAs anytime ≤ 2 weeks (or 5 half-lives, whichever is longer) prior to start of study treatment.

5. Systemic chronic corticosteroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy within 7 days of first dose of study treatment. Topical, inhaled, nasal and ophthalmic steroids are allowed.

6. For arms containing canakinumab: Participants with ANC < 500 /µL

Participant Flow Table

Overall Study

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W	Total
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W	
Started	17	6	8	2	33
Completed	0	0	0	0	0
Not Completed*	17	6	8	2	33

Adverse Event	1	0	1	0	2
Physician Decision	14	4	4	2	24
Progressive Disease	2	1	1	0	4
Patient Decision	0	0	2	0	2
Planned Bone Marrow Transplant	0	1	0	0	1

* Not completed refers to treatment discontinuation. The reasons for discontinuation are listed below.

Baseline Characteristics

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W	Total
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W	
Number of Participants [units: participants]	17	6	8	2	33
Baseline Analysis Population Description					
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation					
	71.8±8.31	66.5±16.99	67.9±9.25	75.5±0.71	70.1±10.26
Age, Customized (units: Participants)					

Analysis Population Type: Participants Count of Participants (Not Applicable)					
18 – <65 years	4	2	4	0	10
≥65 – <85 years	12	4	4	2	22
≥ 85 years	1	0	0	0	1
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Female	7	2	2	0	11
Male	10	4	6	2	22
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Asian	3	2	0	1	6
White	14	4	8	1	27
Study Specific Characteristic **Baseline red blood cell transfusion independence status (16 weeks)** (units: Participants) Description: Transfusion status at baseline was considered for 16-week intervals and defined as follows: • Transfusion independent, defined as receiving no transfusions in the 16 weeks prior to Cycle 1 Day 1 (C1D1). • Transfusion dependent with high transfusion burden, defined as receiving ≥ 8 units / 16 weeks prior to C1D1. • Transfusion dependent with low transfusion burden, defined as receiving < 8 units / 16 weeks prior to C1D1. Analysis Population Type: Participants Count of Participants (Not Applicable)					
Transfusion independent	3	0	2	0	5
Low burden dependence	5	2	0	2	9
High burden dependence	9	4	6	0	19
Study Specific Characteristic **Baseline platelet transfusion independence status (16 weeks)** (units: Participants) Description: Transfusion status at baseline was considered for 16-week intervals and defined as follows: • Transfusion independent, defined as receiving no transfusions in the 16 weeks prior to Cycle 1 Day 1 (C1D1). • Transfusion dependent with high transfusion burden, defined as receiving ≥ 8 units / 16 weeks					

prior to C1D1. • Transfusion dependent with low transfusion burden, defined as receiving < 8 units / 16 weeks prior to C1D1.
Analysis Population Type: Participants
Count of Participants (Not Applicable)

Transfusion independent	15	6	7	2	30
Low burden dependence	1	0	0	0	1
High burden dependence	1	0	1	0	2

Primary Outcome Result(s)

Number of participants with Dose-Limiting Toxicities (DLTs)

Description	A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first two cycles (42 days for Q3W or 56 days for Q4W) of treatment for each study arm. Other clinically significant toxicities may be considered to be DLTs, even if not CTCAE grade 3 or higher.
Time Frame	42 days for Q3W schedule and 56 days for Q4W schedule
Analysis Population Description	The dose determining set included all participants who received at least one dose of study treatment and who met the minimum exposure criterion defined in the protocol and had sufficient safety evaluations or experienced a DLT during the DLT evaluation period.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	6	1

Number of participants with Dose-Limiting Toxicities (DLTs) (units: participants)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)	Count of Participants (Percentage)
At least one DLT	1 (5.88%)	0 (%)	1 (16.67%)	0 (%)
- Chest discomfort	1 (5.88%)	0 (%)	0 (%)	0 (%)
- Infusion site reaction	0 (%)	0 (%)	1 (16.67%)	0 (%)

Number of participants with AEs and SAEs during the on-treatment period

Description	Number of participants with AEs (any adverse events regardless of seriousness) and serious adverse events (SAEs), including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs. AE grades to characterize the severity of the AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For CTCAE v5.0, Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE. The on-treatment period is defined from the day of first administration of any study treatment up to 30 days after the date of the last actual administration of any study drug.
Time Frame	From first dose of study treatment to 30 days after last dose, up to approximately 77 weeks
Analysis Population Description	All participants who received at least one dose of study treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2

Number of participants with AEs and SAEs during the on-treatment period (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
AEs	16 (94.12%)	6 (100%)	8 (100%)	2 (100%)
Treatment-related AEs	9 (52.94%)	3 (50%)	3 (37.5%)	0 (%)
AEs with grade>=3	9 (52.94%)	3 (50%)	3 (37.5%)	1 (50%)
Treatment-related AEs with grade>=3	4 (23.53%)	0 (%)	2 (25%)	0 (%)
SAEs	3 (17.65%)	3 (50%)	1 (12.5%)	1 (50%)
Treatment-related SAEs	0 (%)	0 (%)	1 (12.5%)	0 (%)

Number of participants with dose reductions and dose interruptions of MBG453

Description	Number of participants with at least one dose reduction and at least one dose interruption of MBG453. Dose adjustments were permitted for participants who did not tolerate the protocol-specified dosing schedule.
Time Frame	Up to approximately 48 weeks
Analysis Population Description	All participants who received at least one dose of MBG453.

	MBG453 800 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	2

Number of participants with dose reductions and dose interruptions of MBG453 (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
At least one dose reduction or interruption	1 (5.88%)	0 (%)
At least one dose reduction	1 (5.88%)	0 (%)
At least one dose interruption	0 (%)	0 (%)

Number of participants with dose reductions and dose interruptions of canakinumab

Description	Number of participants with at least one dose reduction and at least one dose interruption of canakinumab. Dose adjustments were permitted for participants who did not tolerate the protocol-specified dosing schedule.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of canakinumab.

	Canakinumab 250 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	6	2
Number of participants with dose reductions and dose interruptions of canakinumab (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
At least one dose reduction or interruption	1 (16.67%)	0 (%)
At least one dose reduction	1 (16.67%)	0 (%)

At least one dose interruption	0 (%)	0 (%)

Number of participants with dose reductions and dose interruptions of NIS793

Description	Number of participants with at least one dose reduction and at least one dose interruption of NIS793. Dose adjustments were permitted for participants who did not tolerate the protocol-specified dosing schedule.
Time Frame	Up to approximately 51 weeks
Analysis Population Description	All participants who received at least one dose of NIS793

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	8
Number of participants with dose reductions and dose interruptions of NIS793 (units: participants)	**Count of Participants (Percentage)**
At least one dose reduction or interruption	3 (37.5%)
At least one dose reduction	3 (37.5%)
At least one dose interruption	0 (%)

Dose intensity of MBG453

Description	Dose intensity of MBG453 was calculated as cumulative actual dose in milligrams divided by duration of exposure in days and multiplied by 28 days.
Time Frame	Up to approximately 48 weeks

Analysis Population Description	All participants who received at least one dose of MBG453.

	MBG453 800 mg Q4W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	2
Dose intensity of MBG453 (units: mg per cycle (28 days))	**Median (Full Range)**	**Median (Full Range)**
	780.1 (688 to 804)	801.8 (800 to 804)

Dose intensity of canakinumab

Description	Dose intensity of canakinumab was calculated as cumulative actual dose in milligrams divided by duration of exposure in days and multiplied by 28 days.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of canakinumab.

	Canakinumab 250 mg Q4W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	6	2

Dose intensity of canakinumab (units: mg per cycle (28 days))	**Median (Full Range)**	**Median (Full Range)**
	248.0 (211 to 252)	250.6 (250 to 251)

Dose intensity of NIS793

Description	Dose intensity of NIS793 was calculated as cumulative actual dose in milligrams divided by duration of exposure in days and multiplied by 21 days.
Time Frame	Up to approximately 51 weeks
Analysis Population Description	All participants who received at least one dose of NIS793.

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	8
Dose intensity of NIS793 (units: mg per cycle (21 days))	**Median (Full Range)**
	1400.0 (1105 to 1400)

Secondary Outcome Result(s)

Change from baseline in red blood cells (RBC) transfusions

Description	The mean change from baseline in RBC transfusions over a fixed timeframe was summarized by time using descriptive statistics. The fixed timeframe for this endpoint included Week 8 to Week 16, and Week 8 to Week 24. The participants baseline transfusion rate was based on the transfusions received during the 16-week period prior to the start of study treatment (expressed as transfusions per 8 weeks, averaged

over two 8-week periods). The change from baseline in RBC transfusions was expressed as packed RBC units per 8 weeks (averaged over two 8-week periods for the timeframe Week 8 to Week 16).

Time Frame: Baseline to Week 8-16 and baseline to Week 8-24

Analysis Population Description: All participants who received at least one dose of the study treatment, were RBC transfusion-dependent at baseline, and had an available value for the outcome measure at each fixed timeframe.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	12	6	6	1
Change from baseline in red blood cells (RBC) transfusions (units: packed RBC units per 8 weeks)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Baseline to Week 8-16 (n=12,6,6,1)	3.3 ± 7.00	0.8 ± 2.04	-0.5 ± 3.83	5.0
Baseline to Week 8-24 (n=12,6,6,1)	2.0 ± 4.59	-0.3 ± 2.07	-4.4 ± 3.02	4.0

Change from baseline in platelet transfusions

Description: The mean change from baseline in platelet transfusions over a fixed timeframe was summarized by time using descriptive statistics. The fixed timeframe for this endpoint included Week 8 to Week 16, and Week 8 to Week 24. The participants baseline transfusion rate was based on the transfusions received during the 16-week period prior to the start of study treatment (expressed as transfusions per 8 weeks, averaged over two 8-week periods). The change from baseline in platelet transfusions was expressed as platelet units per 8 weeks (averaged over two 8-week periods for the timeframe Week 8 to Week 16).

Time Frame: Baseline to Week 8-16 and baseline to Week 8-24

Analysis Population Description	All participants who received at least one dose of the study treatment, were platelet transfusion-dependent at baseline, and had an available value for the outcome measure at each fixed timeframe.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	2	0	1	0
Change from baseline in platelet transfusions (units: platelet units per 8 weeks)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Baseline to Week 8-16 (n=2,0,1,0)	23.0 ± 33.23		-1.0	
Baseline to Week 8-24 (n=2,0,1,0)	14.5 ± 21.92		-6.0	

Duration of packed RBC and platelet transfusion independence

Description	Transfusion independence is defined as no transfusion for any consecutive 56 days or longer during the treatment period in participants who were transfusion dependent at baseline. Duration of transfusion independence was analyzed using the Kaplan-Meier method.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who were RBC or platelet transfusion dependent at baseline within 16 weeks prior to study treatment initiation and achieved transfusion independence for at least any 56 consecutive days. No participants achieved transfusion independence.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	0	0	0	0
Duration of packed RBC and platelet transfusion independence (units: days)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**

Time to onset of transfusion independence

Description	Transfusion independence is defined as no transfusion for any consecutive 56 days or longer during the treatment period in participants who were transfusion dependent at baseline. Time to onset of transfusion independence was analyzed using the Kaplan-Meier method.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who were RBC or platelet transfusion dependent at baseline within 16 weeks prior to study treatment initiation and achieved transfusion independence for at least any 56 consecutive days. No participants achieved transfusion independence.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W

Number of Participants Analyzed [units: participants]	0	0	0	0
Time to onset of transfusion independence (units: days)	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**	**Median (Full Range)**

Change from baseline in hemoglobin

Description	Hemoglobin levels were measured in blood samples. Since the majority of participants required RBC transfusions during the study, these results are confounded and should be interpreted with caution.
Time Frame	From baseline to end of treatment, up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment and had an available value for the outcome measure at baseline and at the end of treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	11	5	6	1
Change from baseline in hemoglobin (units: gram/liter (g/L))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-3.2 ± 12.55	4.0 ± 5.70	0.0 ± 8.51	6.0

Change from baseline in platelets

Description	Platelet count was measured in blood samples.
Time Frame	From baseline to end of treatment, up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment and had an available value for the outcome measure at baseline and at the end of treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	11	5	6	1
Change from baseline in platelets (units: platelets*10^9/liter(L))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-4.9 ± 34.99	-40.4 ± 35.71	29.8 ± 34.95	-221.0

Change from baseline in leukocytes

Description	Leucocyte count was measured in blood samples.
Time Frame	From baseline to end of treatment, up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment and had an available value for the outcome measure at baseline and at the end of treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	11	5	6	1
Change from baseline in leukocytes (units: leukocytes*10^9/liter(L))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-0.3 ± 1.27	-0.2 ± 1.09	0.3 ± 1.72	0.1

Change from baseline in neutrophils

Description	Neutrophil count was measured in blood samples.
Time Frame	From baseline to end of treatment, up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment and had an available value for the outcome measure at baseline and at the end of treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W

Number of Participants Analyzed [units: participants]	11	5	6	1
Change from baseline in neutrophils (units: neutrophils*10^9/liter(L))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-0.2 ± 0.95	-0.3 ± 0.80	0.2 ± 1.31	0.5

Best Overall Response (BOR) per IWG

Description	Response evaluation was based on the investigator's assessment. Response criteria in myelodysplastic syndrome (MDS) were based on the revised recommendations of the international working group (IWG) for diagnosis, standardization of response criteria, treatment outcome, and reporting standards for therapeutic trials in MDS. Evaluation of response rely primarily on blood and bone marrow assessments, as well as on the presence or absence of extramedullary disease. The best overall disease response was the best disease response recorded from the start of the treatment until disease progression/relapse. BOR of complete remission (CR), complete remission with partial hematologic recovery (CRh), marrow complete remission (mCR), partial remission (PR), and stable disease (SD) were confirmed in the evaluation of BOR.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Best Overall Response (BOR) per IWG (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**

Complete Remission (CR)	0 (%)	0 (%)	0 (%)	0 (%)
Complete Remission with partial hematologic recovery (CRh)	0 (%)	0 (%)	0 (%)	0 (%)
Marrow Complete Remission (mCR)	1 (5.88%)	1 (16.67%)	0 (%)	0 (%)
Partial Remission (PR)	0 (%)	0 (%)	0 (%)	0 (%)
Stable Disease (SD)	11 (64.71%)	3 (50%)	1 (12.5%)	1 (50%)
Relapse after CR or PR	0 (%)	0 (%)	0 (%)	0 (%)
Progressive Disease (PD)	2 (11.76%)	1 (16.67%)	1 (12.5%)	0 (%)
Unknown (UNK)	3 (17.65%)	1 (16.67%)	6 (75%)	1 (50%)

Overall Response Rate (ORR) per IWG

Description	ORR is the percentage of participants with a confirmed best overall response of complete remission (CR), complete remission with partial hematologic recovery (CRh), marrow complete remission (mCR) or partial remission (PR), based on local investigator assessment per IWG.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.)	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with

		injection at the dose of 250 mg Q4W		canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Overall Response Rate (ORR) per IWG (units: percentage of participants)	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**
	5.9 (0.3 to 25.0)	16.7 (0.9 to 58.2)	0 (0.0 to 31.2)	0 (0.0 to 77.6)

Hematologic improvement per IWG

Description	Response evaluation was based on the investigator's assessment. Response criteria in MDS were based on the revised recommendations of the IWG for diagnosis, standardization of response criteria, treatment outcome, and reporting standards for therapeutic trials in MDS. Hematologic improvement (HI) was captured in the following categories: erythroid response (HI-E), platelet response (HI-P), neutrophil response (HI-N) and no HI or unknown. A patient can be counted in more than one category; for instance, a patient can achieve both HI-E and HI-P. Since the majority of participants required RBC transfusions during the study, these results are confounded and should be interpreted with caution.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2

Hematologic improvement per IWG (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Erythroid response (HI-E)	1 (5.88%)	0 (%)	0 (%)	0 (%)
Platelet response (HI-P)	1 (5.88%)	0 (%)	0 (%)	0 (%)
Neutrophil response (HI-N)	0 (%)	0 (%)	0 (%)	0 (%)
No HI or Unknown	16 (94.12%)	6 (100%)	8 (100%)	2 (100%)

Hematologic improvement rate per IWG

Description	Hematologic improvement rate is the percentage of participants with a hematologic improvement of erythroid response (HI-E), platelet response (HI-P) or neutrophil response (HI-N), based on local investigator assessment per IWG. Since the majority of participants required RBC transfusions during the study, these results are confounded and should be interpreted with caution.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2

Hematologic improvement rate per IWG (units: percentage of participants)	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**
	5.9 (0.3 to 25.0)	0 (0.0 to 39.3)	0 (0.0 to 31.2)	0 (0.0 to 77.6)

Cytogenetic response per IWG

Description	Response evaluation was based on the investigator's assessment. Response criteria in MDS were based on the revised recommendations of the IWG for diagnosis, standardization of response criteria, treatment outcome, and reporting standards for therapeutic trials in MDS. Cytogenetic response was captured in the following categories: complete remission (CR), partial remission (PR), not applicable and unknown.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Cytogenetic response per IWG (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Complete Remission (CR)	1 (5.88%)	0 (%)	0 (%)	0 (%)
Partial Remission (PR)	0 (%)	0 (%)	0 (%)	0 (%)

No response	2 (11.76%)	1 (16.67%)	0 (%)	0 (%)
Not applicable	14 (82.35%)	4 (66.67%)	5 (62.5%)	1 (50%)
Unknown	0 (%)	1 (16.67%)	3 (37.5%)	1 (50%)

Cytogenetic response rate per IWG

Description	Cytogenetic response rate is the percentage of participants with a cytogenetic response of complete remission (CR) or partial remission (PR), based on local investigator assessment per IWG.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	**Canakinumab 250 mg Q4W**	**NIS793 1400 mg Q3W**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Cytogenetic response rate per IWG (units: percentage of participants)	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**	**Number (90% Confidence Interval)**
	5.9 (0.3 to 25.0)	0 (0.0 to 39.3)	0 (0.0 to 31.2)	0 (0.0 to 77.6)

Time to onset of BOR

Description	Time to onset of BOR is defined as the time between date of start of study treatment to the date of first onset of partial remission (PR) or better response. Time to onset of BOR was analyzed using the Kaplan-Meier method if there were at least 10 participants treated in the same treatment arm.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Time to onset of BOR (units: months)	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**
	NA (NA to NA)[1]	NA (NA to NA)[2]	NA (NA to NA)[2]	NA (NA to NA)[2]

[1] Not estimable due to insufficient number of participants with events.
[2] Not estimable due to insufficient number of treated participants in the arm (n<10).

Duration of Response (DOR)

Description	DOR is defined as the duration from the first documented onset of complete remission (CR), complete remission with partial hematologic recovery (CRh), marrow complete remission (mCR) or partial remission (PR) to the date of progressive disease (PD) or relapse or death due to MDS. DOR only applies to participants with a best overall response of CR, CRh, mCR or PR by investigator assessment per IWG. DOR was analyzed using the Kaplan-Meier method if there were at least 10 responders in the same treatment arm.

Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment and achieved a best overall response of CR, CRh, mCR or PR.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	1	1	0	0
Duration of Response (DOR) (units: months)	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**
	NA (NA to NA)[1]	NA (NA to NA)[1]		

[1] Not estimable due to insufficient number of responders (n<10).

Progression-free survival (PFS)

Description	PFS is defined as the time from the start of treatment until death due to any reason, disease progression, or relapse, whichever comes first. PFS was analyzed using the Kaplan-Meier method if there were at least 10 participants treated in the same treatment arm.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Progression-free survival (PFS) (units: months)	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**
	NA (6.4 to NA)[1]	NA (NA to NA)[2]	NA (NA to NA)[2]	NA (NA to NA)[2]

[1] Not estimable due to insufficient number of participants with events.
[2] Not estimable due to insufficient number of treated participants in the arm (n<10).

Time to progression (TTP)

Description	TTP is the time from the start of treatment to the date of progressive disease (PD), relapse or death due to underlying cancer. TTP was analyzed using the Kaplan-Meier method if there were at least 10 participants treated in the same treatment arm.
Time Frame	Up to approximately 73 weeks
Analysis Population Description	All participants who received at least one dose of the study treatment.

	MBG453 800 mg Q4W	Canakinumab 250 mg Q4W	NIS793 1400 mg Q3W	MBG453 800 mg Q4W + canakinumab 250 mg Q4W
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion	Canakinumab administered by subcutaneous (s.c.)	NIS793 administered by i.v. infusion at the dose of	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with

	at the dose of 800 mg every 4 weeks (Q4W)	injection at the dose of 250 mg Q4W	1400 mg every 3 weeks (Q3W)	canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	6	8	2
Time to progression (TTP) (units: months)	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**	**Median (90% Confidence Interval)**
	NA (6.4 to NA)[1]	NA (NA to NA)[2]	NA (NA to NA)[2]	NA (NA to NA)[2]

[1] Not estimable due to insufficient number of participants with events.
[2] Not estimable due to insufficient number of treated participants in the arm (n<10).

Maximum observed serum concentration (Cmax) of MBG453

Description	Pharmacokinetic (PK) parameters were calculated based on MBG453 serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 3: pre-infusion, end of infusion, 6 hours, 168 hours (Cycle 1 only), and 672 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received MBG453 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	MBG453 800 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	16	2
Maximum observed serum concentration (Cmax) of MBG453 (units: µg/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=16,2)	215 ± 64.2	207 ± 21.2
Cycle 3 (n=15,1)	256 ± 81.7	225

Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of MBG453

Description	PK parameters were calculated based on MBG453 serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for area under the curve (AUC) calculation.
Time Frame	Cycle 1 and Cycle 3: pre-infusion, end of infusion, 6 hours, 168 hours (Cycle 1 only), and 672 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received MBG453 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	MBG453 800 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	16	2
Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of MBG453 (units: day*µg/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=16,2)	2210 ± 732	1470 ± 486
Cycle 3 (n=15,1)	3810 ± 1770	3580

Trough serum concentration (Ctrough) of MBG453

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycles 5, 6, 9 and 12: pre-dose on Day 1. One cycle=28 days

Analysis Population Description	Participants in the pharmacokinetic analysis set who received MBG453 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	MBG453 800 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	14	1
Trough serum concentration (Ctrough) of MBG453 (units: µg/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 5 Day 1 (n=14,1)	64.3 ± 31.8	23.6
Cycle 6 Day 1 (n=13,1)	68.4 ± 39.2	26
Cycle 9 Day 1 (n=2,0)	87.2 ± 14.6	
Cycle 12 Day 1 (n=1,0)	78.5	

Maximum observed serum concentration (Cmax) of canakinumab

Description	PK parameters were calculated based on canakinumab serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 168 hours (Cycle 1 only), and 672 hours after dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received canakinumab and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	Canakinumab 250 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**

Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	6	2
Maximum observed serum concentration (Cmax) of canakinumab (units: µg/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 1 (n=6,2)	11.4 ± 4.49	16.5 ± 9.05
Cycle 3 (n=6,1)	13 ± 3.21	9.13

Time to maximum observed serum concentration (Tmax) of canakinumab

Description	PK parameters were calculated based on canakinumab serum concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) observed concentration following a dose. Actual sampling times were considered for the calculation of PK parameters.
Time Frame	Cycle 1 and Cycle 3: pre-dose, 168 hours (Cycle 1 only), and 672 hours after dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received canakinumab and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	Canakinumab 250 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	6	2
Time to maximum observed serum concentration (Tmax) of canakinumab (units: hours)	**Median (Full Range)**	**Median (Full Range)**
Cycle 1 (n=6,2)	163 (163 to 837)	152 (139 to 165)
Cycle 3 (n=6,1)	0 (0 to 670)	671 (671 to 671)

Trough serum concentration (Ctrough) of canakinumab

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycles 5, 6, 9, 12, 15 and 18: pre-dose on Day 1. One cycle=28 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received canakinumab and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	Canakinumab 250 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	5	1
Trough serum concentration (Ctrough) of canakinumab (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Cycle 5 Day 1 (n=5,1)	15000 ± 2930	10000
Cycle 6 Day 1 (n=5,1)	17300 ± 6950	8370
Cycle 9 Day 1 (n=3,0)	17400 ± 6250	
Cycle 12 Day 1 (n=3,0)	14500 ± 6860	
Cycle 15 Day 1 (n=1,0)	19800	
Cycle 18 Day 1 (n=1,0)	17100	

Maximum observed serum concentration (Cmax) of NIS793

Description	Pharmacokinetic (PK) parameters were calculated based on NIS793 serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.

Time Frame	Cycle 1 and Cycle 3: pre-infusion, end of infusion, 6 hours, 168 hours (Cycle 1 only), and 504 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=21 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received NIS793 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	7
Maximum observed serum concentration (Cmax) of NIS793 (units: µg/mL)	**Mean ± Standard Deviation**
Cycle 1 (n=7)	320 ± 91.6
Cycle 3 (n=5)	385 ± 61

Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of NIS793

Description	PK parameters were calculated based on NIS793 serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for area under the curve (AUC) calculation.
Time Frame	Cycle 1 and Cycle 3: pre-infusion, end of infusion, 6 hours, 168 hours (Cycle 1 only), and 504 hours after the end of the infusion on Day 1. The duration of the infusion was 30 minutes. One cycle=21 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received NIS793 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)

Number of Participants Analyzed [units: participants]	7
Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of NIS793 (units: day*µg/mL)	**Mean ± Standard Deviation**
Cycle 1 (n=7)	2460 ± 824
Cycle 3 (n=5)	3530 ± 2030

Trough serum concentration (Ctrough) of NIS793

Description	Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	Cycles 5, 6, 10 and 14: pre-dose on Day 1. One cycle=21 days
Analysis Population Description	Participants in the pharmacokinetic analysis set who received NIS793 and had an available value for the outcome measure at the corresponding treatment cycle. The pharmacokinetic analysis set consisted of all participants with at least one available valid PK concentration measurement, who received any study drug and had no protocol deviations that impacted PK data.

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	4
Trough serum concentration (Ctrough) of NIS793 (units: ng/mL)	**Mean ± Standard Deviation**
Cycle 5 Day 1 (n=4)	64600 ± 57100
Cycle 6 Day 1 (n=2)	256000 ± 266000
Cycle 10 Day 1 (n=1)	63900
Cycle 14 Day 1 (n=1)	60100

NOVARTIS

Number of participants with anti-MBG453 antibodies

Description	The immunogenicity (IG) against MBG453 was assessed in serum using a validated homogeneous enzyme-linked immunosorbent assay (ELISA). Patient anti-drug antibodies (ADA) status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline sample, all of which are ADA-negative samples • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample • Treatment-boosted ADA-positive = ADA-positive sample at baseline and at least 1 treatment-boosted ADA-positive sample
Time Frame	Baseline (before first dose) and post-baseline (assessed throughout the treatment up to approximately 48 weeks).
Analysis Population Description	Participants who received MBG453 with a non-missing baseline IG sample and at least one non-missing post-baseline IG sample.

	MBG453 800 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	17	1
Number of participants with anti-MBG453 antibodies (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
ADA-negative at baseline	16 (94.12%)	0 (%)
ADA-positive at baseline	1 (5.88%)	1 (100%)
ADA-negative post-baseline	13 (76.47%)	0 (%)
Treatment-induced ADA-positive	3 (17.65%)	0 (%)
Treatment-boosted ADA-positive	0 (%)	0 (%)

NOVARTIS

Number of participants with anti-canakinumab antibodies

Description	The immunogenicity (IG) against canakinumab was assessed in serum using a validated Meso Scale Discovery (MSD) electrochemiluminescence assay. Patient anti-drug antibodies (ADA) status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline sample, all of which are ADA-negative samples • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample • Treatment-boosted ADA-positive = ADA-positive sample at baseline and at least 1 treatment-boosted ADA-positive sample
Time Frame	Baseline (before first dose) and post-baseline (assessed throughout the treatment up to approximately 73 weeks).
Analysis Population Description	Participants who received canakinumab with a non-missing baseline IG sample and at least one non-missing post-baseline IG sample.

	Canakinumab 250 mg Q4W	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W**
Arm/Group Description	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W
Number of Participants Analyzed [units: participants]	6	1
Number of participants with anti-canakinumab antibodies (units: participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
ADA-negative at baseline	6 (100%)	1 (100%)
ADA-positive at baseline	0 (%)	0 (%)
ADA-negative post-baseline	6 (100%)	1 (100%)
Treatment-induced ADA-positive	0 (%)	0 (%)
Treatment-boosted ADA-positive	0 (%)	0 (%)

NOVARTIS

Number of participants with anti-NIS793 antibodies

Description	The immunogenicity (IG) against canakinumab was assessed in serum using a validated immuno-assay. Patient anti-drug antibodies (ADA) status was defined as follows: • ADA-negative at baseline: ADA-negative sample at baseline • ADA-positive at baseline: ADA-positive sample at baseline • ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline sample, all of which are ADA-negative samples • Treatment-induced ADA-positive = ADA-negative sample at baseline and at least 1 treatment-induced ADA-positive sample • Treatment-boosted ADA-positive = ADA-positive sample at baseline and at least 1 treatment-boosted ADA-positive sample
Time Frame	Baseline (before first dose) and post-baseline (assessed throughout the treatment up to approximately 51 weeks).
Analysis Population Description	Participants who received NIS793 with a non-missing baseline IG sample and at least one non-missing post-baseline IG sample.

	NIS793 1400 mg Q3W
Arm/Group Description	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)
Number of Participants Analyzed [units: participants]	7
Number of participants with anti-NIS793 antibodies (units: participants)	**Count of Participants (Percentage)**
ADA-negative at baseline	7 (100%)
ADA-positive at baseline	0 (%)
ADA-negative post-baseline	7 (100%)
Treatment-induced ADA-positive	0 (%)
Treatment-boosted ADA-positive	0 (%)

Safety Results

Time Frame	On- and post-treatment safety follow-up: from first dose of study treatment to 130 days after last dose of canakinumab and 150 days after last dose of MBG45 and NIS793, up to approximately 91 weeks.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	MBG453 800 mg Q4W N = 17	**Canakinumab 250 mg Q4W N = 6**	**NIS793 1400 mg Q3W N = 8**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W N = 2**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Total Number Affected	0	0	0	0
Total Number At Risk	17	6	8	2

Serious Adverse Events

Time Frame	On- and post-treatment safety follow-up: from first dose of study treatment to 130 days after last dose of canakinumab and 150 days after last dose of MBG45 and NIS793, up to approximately 91 weeks.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

	MBG453 800 mg Q4W N = 17	**Canakinumab 250 mg Q4W N = 6**	**NIS793 1400 mg Q3W N = 8**	**MBG453 800 mg Q4W + canakinumab 250 mg Q4W N = 2**
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Total # Affected by any Serious Adverse Event	3	3	1	1
Total # at Risk by any Serious Adverse Event	17	6	8	2
Blood and lymphatic system disorders				
Anaemia	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders				
Constipation	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
General disorders and administration site conditions				

Chest pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Cellulitis	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (50.00%)
Injury, poisoning and procedural complications				
Subdural haematoma	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	On- and post-treatment safety follow-up: from first dose of study treatment to 130 days after last dose of canakinumab and 150 days after last dose of MBG45 and NIS793, up to approximately 91 weeks.
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	MBG453 800 mg Q4W N = 17	Canakinumab 250 mg Q4W N = 6	NIS793 1400 mg Q3W N = 8	MBG453 800 mg Q4W + canakinumab 250 mg Q4W N = 2
Arm/Group Description	MBG453 administered by intravenous (i.v.) infusion at the dose of 800 mg every 4 weeks (Q4W)	Canakinumab administered by subcutaneous (s.c.) injection at the dose of 250 mg Q4W	NIS793 administered by i.v. infusion at the dose of 1400 mg every 3 weeks (Q3W)	MBG453 administered by i.v. infusion at the dose of 800 mg Q4W in combination with canakinumab s.c. at the dose of 250 mg Q4W
Total # Affected by any Other Adverse Event	16	6	8	1
Total # at Risk by any Other Adverse Event	17	6	8	2
Blood and lymphatic system disorders				
Anaemia	4 (23.53%)	4 (66.67%)	2 (25.00%)	1 (50.00%)
Haemorrhagic diathesis	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Leukocytosis	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Leukopenia	2 (11.76%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Lymphopenia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutropenia	2 (11.76%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Thrombocytopenia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders				
Atrial fibrillation	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Cardiac failure acute	1 (5.88%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Cardiac failure congestive	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Myocardial infarction	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Palpitations	1 (5.88%)	0 (0.00%)	0 (0.00%)	1 (50.00%)
Ear and labyrinth disorders				

Tinnitus	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endocrine disorders				
Hyperthyroidism	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypothyroidism	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders				
Blepharitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (50.00%)
Cataract	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vision blurred	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders				
Colitis	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Constipation	1 (5.88%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Diarrhoea	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dry mouth	1 (5.88%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Dyspepsia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysphagia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Flatulence	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gingival bleeding	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Gingival pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Mouth ulceration	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Nausea	1 (5.88%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Tongue oedema	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Toothache	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

General disorders and administration site conditions				
Administration site extravasation	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Asthenia	2 (11.76%)	2 (33.33%)	3 (37.50%)	0 (0.00%)
Catheter site bruise	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest discomfort	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chills	1 (5.88%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Fatigue	3 (17.65%)	0 (0.00%)	1 (12.50%)	1 (50.00%)
Infusion site reaction	0 (0.00%)	0 (0.00%)	2 (25.00%)	0 (0.00%)
Malaise	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	1 (5.88%)	0 (0.00%)	2 (25.00%)	0 (0.00%)
Pain	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Peripheral swelling	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Pyrexia	1 (5.88%)	1 (16.67%)	2 (25.00%)	0 (0.00%)
Vaccination site reaction	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders				
Hyperbilirubinaemia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
COVID-19	4 (23.53%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Furuncle	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Hordeolum	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral herpes	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)

Pneumonia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory tract infection	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Contusion	2 (11.76%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Fall	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infusion related reaction	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Limb injury	1 (5.88%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Transfusion-related circulatory overload	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Vascular injury	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Investigations				
Activated partial thromboplastin time prolonged	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alanine aminotransferase increased	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Aspartate aminotransferase increased	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood alkaline phosphatase increased	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood bilirubin increased	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood creatinine increased	4 (23.53%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase increased	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
International normalised ratio increased	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphocyte count decreased	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutrophil count decreased	4 (23.53%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Platelet count decreased	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Weight decreased	0 (0.00%)	1 (16.67%)	1 (12.50%)	0 (0.00%)

White blood cell count decreased	3 (17.65%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders				
Decreased appetite	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Folate deficiency	0 (0.00%)	0 (0.00%)	1 (12.50%)	1 (50.00%)
Hyperglycaemia	5 (29.41%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hyperkalaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypocalcaemia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypokalaemia	0 (0.00%)	2 (33.33%)	0 (0.00%)	0 (0.00%)
Hypomagnesaemia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hyponatraemia	2 (11.76%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypophosphataemia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Iron deficiency	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Iron overload	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular weakness	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myalgia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Pain in extremity	1 (5.88%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Nervous system disorders				
Cerebrovascular accident	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Dizziness	2 (11.76%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Dysgeusia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				

Agitation	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Anxiety	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Confusional state	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Insomnia	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders				
Cystitis haemorrhagic	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Dysuria	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haematuria	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Micturition urgency	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nocturia	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Renal colic	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Renal impairment	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Cough	4 (23.53%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dyspnoea	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epistaxis	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oropharyngeal pain	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural effusion	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Productive cough	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary oedema	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Rhinitis allergic	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rhinorrhoea	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper-airway cough syndrome	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Skin and subcutaneous tissue disorders				
Ecchymosis	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Perioral dermatitis	1 (5.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus	3 (17.65%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rash	2 (11.76%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Skin ulcer	0 (0.00%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Vascular disorders				
Haematoma	2 (11.76%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypertension	1 (5.88%)	1 (16.67%)	0 (0.00%)	0 (0.00%)
Hypotension	1 (5.88%)	0 (0.00%)	1 (12.50%)	0 (0.00%)
Peripheral artery occlusion	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)

Conclusion:

The study CMBG453E12101 was initially conceived to evaluate the safety/tolerability and clinical activity of MBG453 in combination with canakinumab or NIS793 for the treatment of participants with lower to intermediate risk myelodysplastic syndromes (LIR-MDS) for whom there were no standard of care treatment options.

In 2020, following a review of the study protocol, the FDA recommended Novartis to first evaluate the safety/tolerability and clinical activity of single agents MBG453, canakinumab and NIS793 individually in participants with LIR-MDS prior to commencing the evaluation of MBG453-based combinations. As a result, the design of this study was revised to accommodate 2 single agent treatment arms to confirm the dosage of MBG453 and canakinumab, and 1 dose escalation treatment arm to determine the optimal dosage of NIS793 for the treatment of participants with LIR-MDS. Two combination treatment arms were also retained and would commence patient enrollment provided no untoward safety signals would be identified in the single agent treatment arms.

Six participants were treated with canakinumab 250 mg Q4W, and 8 participants were treated with NIS793 1400 mg Q3W. Initially, 6 participants were treated with MBG453 800 mg Q4W and subsequently 11 more participants were treated with MBG453 800 mg Q4W in an enrichment cohort to further evaluate the agent's tolerability and clinical activity. No new safety signal emerged from the single agent treatment arms. DLT was reported in 1 patient in the MBG453 800 mg Q4W arm which led to study medication discontinuation, and in 1 patient in the NIS793 1400 mg Q3W arm which led to a dose reduction. Few participants required study treatment dose reduction and/or dose interruption due to adverse events.

The PK characteristics of MBG453, canakinumab and NIS793 were consistent with historical data. ADA-positive incidence was 17.6% in the MBG453 800 mg Q4W arm and 0% in the other three treatment arms.

Following review of patient data in conjunction with the investigators, it was concluded that canakinumab 250 mg Q4W would be safe to combine with MBG453 800 mg Q4W. A decision was made not to dose escalate NIS793 beyond 1400 mg Q3W because 1 patient experienced DLT and it was considered safe to combine NIS793 1400 mg Q3W with MBG453 600 mg Q3W. Consequently, 2 participants were treated with MBG453 800 mg Q4W in combination with canakinumab 250 mg Q4W before an enrollment halt was implemented late in 2022. In total, 33 participants were treated across 4 treatment arms before a further enrollment halt was implemented in September 2023. Consequently, this study did not enroll any participants to the MBG453 and NIS793 combination treatment arm.

The majority of participants enrolled into this study were RBC transfusion dependent. While mCR was attained by 1 patient each in the MBG453 800 mg Q4W and the canakinumab 250 mg Q4W treatment arm, these responses did not translate into meaningful clinical activity. Specifically, no patient achieved transfusion independence in any of the treatment arms. Varying degrees of change from baseline hemoglobin and platelet levels were observed in participants across the arms. However, because the majority of participants required RBC/platelet transfusion during the study, these findings were confounded and should be interpreted with caution.

Overall, with the small sample sizes of each treatment arm, it is not possible to draw meaningful conclusions regarding the clinical activity of MBG453, canakinumab and NIS793.

NOVARTIS

Date of Clinical Trial Report

10-Dec-2024