Clinical trial results:
Multiple, fixed-dose, comparative efficacy and safety evaluation of RGB-02 and Neulasta® in patients undergoing chemotherapy treatment known to induce neutropenia.

Summary

EudraCT number	2013-003166-14
Trial protocol	CZ HU BG HR
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	RGB-02-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gedeon Richter Plc
Sponsor organisation address	Gyömrői út 19-21, Budapest, Hungary, H-1103
Public contact	Dr. Balázs Lázár, Gedeon Richter Plc., +36 1 432 6437, RA.ctaRichter@richter.hu
Scientific contact	Medical Information Scientific Service, Gedeon Richter Plc., +36 1 5057032, medinfo@richter.hu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2015
Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study was to assess and compare the efficacy and safety of RGB-02 versus Neulasta® (both subcutaneous [s.c.] injections) in breast cancer patients receiving myelosuppressive chemotherapy.

Protection of trial subjects:

This study was conducted in compliance with Independent Ethics Committee (IEC) and the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP-E6) Guidelines, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94 and 2005/28 as enacted into local law, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). In addition, this study was compliant to all local regulatory requirements, and requirements for data protection. Before initiating the study, the Investigator/institution had to have written and dated approval/favorable opinion from the IEC for the study protocol, written Informed Consent Form (ICF), any consent form updates, patient recruitment procedures (e.g., advertisements) and any written information to be provided to patients, and a statement from the IEC that they complied with GCP requirements. The IEC approval had to identify the protocol version as well as the documents reviewed.

Background therapy:

On Day 1 of each cycle, patients received 60 mg/m2 doxorubicin intravenous (i.v.) infusion followed approximately 1 hour later by i.v. infusion of 75 mg/m2 docetaxel. Chemotherapy was repeated every 3 weeks for up to 4 cycles. In each cycle, all patients received standard oral corticosteroid premedication on 3 consecutive days starting on Day -1 (the day before chemotherapy was administered).

Evidence for comparator:

RGB-02 (pegfilgrastim) is an investigational medicinal product (IMP) under development as a biosimilar to the pegfilgrastim Neulasta® which has been approved in the European Union (EU) since 2002 for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes). The active substance of RGB-02 and Neulasta® is a covalent conjugate of recombinant human granulocyte-colony stimulating factor (G-CSF, filgrastim) with a single 20 kDa polyethylene glycol (PEG).

Actual start date of recruitment	28 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Hungary: 48

Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Russian Federation: 84
Country: Number of subjects enrolled	Serbia: 12
Country: Number of subjects enrolled	Ukraine: 55
Worldwide total number of subjects	239
EEA total number of subjects	88

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	234
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 28 January 2014 (first patient first visit) and 08 April 2015 (last patient last visit) a total of 270 patients were screened at 35 of the 40 sites that were opened for this study. Of these, 239 were randomized at 32 sites (in Russia, Hungary, Ukraine, Romania, Czech Republic, Serbia, Bulgaria, Croatia).

Pre-assignment

Screening details:

The study started with a 21-day screening period. During the screening period, the eligibility of the patients to participate in the study was assessed. The randomization was performed on Day -1 or Day 1 of Cycle 1, before chemotherapy administration.

Period 1

Period 1 title	All randomized subjects (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The treatment was administered in a double-blind manner during the first 2 cycles. After the second cycle (from Cycle 3 onwards), the treatment administration became open-label.
Relabeling of Neulasta® syringes and overlabeling of the needle caps of both the test and reference products was used to ensure the blinding. Due to the blinding solution, the syringes for both IMPs were properly blinded so that they were not identifiable either by the pharmacist, the IMP administrator, or the patient

Arms

Are arms mutually exclusive?	Yes
Arm title	RGB-02

Arm description:

All subjects randomized to receive RGB-02 (test product) during Cycles 1-4. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Arm type	Experimental
Investigational medicinal product name	RGB-02
Investigational medicinal product code	RGB-02
Other name	pegfilgrastim 6 mg/0.6 mL (test product)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of RGB-02 pre-filled syringes 6 mg/0.6 mL for subcutaneous (s.c.) administration during Cycles 1-4. Administrated on Day 2 of the cycle approximately 24h after chemotherapy.

Arm title	Neulasta® + RGB-02

Arm description:

All subjects randomized to receive Neulasta® (reference product) during Cycles 1 and 2 under double-blind conditions and who were switched to receive RGB-02 (test product) under open label conditions starting with Cycle 3. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. . A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Arm type	Active comparator
Investigational medicinal product name	Neulasta®
Investigational medicinal product code	
Other name	pegfilgrastim 6 mg/0.6 mL
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of Neulasta® pre-filled syringes 6 mg/0.6 mL for subcutaneous (s.c.) administration during Cycles 1 and 2. Administrated on Day 2 of the cycle approximately 24h after chemotherapy.

Investigational medicinal product name	RGB-02
Investigational medicinal product code	RGB-02
Other name	pegfilgrastim 6 mg/0.6 mL (test product)
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose of RGB-02 pre-filled syringes 6 mg/0.6 mL for subcutaneous (s.c.) administration during Cycles 3 and 4. Administrated on Day 2 of the cycle approximately 24h after chemotherapy.

Number of subjects in period 1	RGB-02	Neulasta® + RGB-02
Started	121	118
Completed	115	109
Not completed	6	9
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	3
Physician decision	1	-
Adverse event, non-fatal	3	3
other	-	3

Baseline characteristics

Reporting groups

Reporting group title	RGB-02

Reporting group description:

All subjects randomized to receive RGB-02 (test product) during Cycles 1-4. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Reporting group title	Neulasta® + RGB-02

Reporting group description:

All subjects randomized to receive Neulasta® (reference product) during Cycles 1 and 2 under double-blind conditions and who were switched to receive RGB-02 (test product) under open label conditions starting with Cycle 3. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. . A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Reporting group values	RGB-02	Neulasta® + RGB-02	Total
Number of subjects	121	118	239
Age categorical Units: Subjects			
Adults (18-64 years)	117	117	234
From 65-84 years	4	1	5
Gender categorical Units: Subjects			
Female	121	118	239
Male	0	0	0

End points

End points reporting groups

Reporting group title	RGB-02

Reporting group description:

All subjects randomized to receive RGB-02 (test product) during Cycles 1-4. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Reporting group title	Neulasta® + RGB-02

Reporting group description:

All subjects randomized to receive Neulasta® (reference product) during Cycles 1 and 2 under double-blind conditions and who were switched to receive RGB-02 (test product) under open label conditions starting with Cycle 3. In addition to the 4 cycles of chemotherapy, 2 additional cycles (Cycles 5-6) with the same regimen were allowed if deemed necessary by the Investigator. For those patients who received more than 4 cycles, RGB-02 was administered as supportive therapy. 3-weeks per cycle. . A Follow-up Visit was performed 6 months (± 10 days) after the first IMP administration.

Subject analysis set title	Per Protocol - RGB-02 (Cycle 1)
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol populations were defined cycle by cycle (Cycles 1 to 4). The PP population for the respective cycle included all patients in the FAS who had no major protocol deviations with a possible impact on the efficacy variables prior to completion of that cycle within the RGB-02 arm.
FAS = Full Analysis Set

Subject analysis set title	Per Protocol - Neulasta® + RGB-02 (Cycle 1)
Subject analysis set type	Per protocol

Subject analysis set description:

Per Protocol populations were defined cycle by cycle (Cycles 1 to 4). The PP population for the respective cycle included all patients in the FAS who had no major protocol deviations with a possible impact on the efficacy variables prior to completion of that cycle within the Neulasta® + RGB-02 arm.
FAS = Full Analysis Set

Subject analysis set title	Full Analysis Set - RGB-02
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who had data for at least one efficacy endpoint within the RGB-02 arm.

Subject analysis set title	Full Analysis Set - Neulasta® + RGB-02
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who had data for at least one efficacy endpoint within the Neulasta® + RGB-02 arm.

Primary: DSN (duration of severe neutropenia) in Cycle 1

End point title	DSN (duration of severe neutropenia) in Cycle 1

End point description:

Duration of severe neutropenia was defined as the number of days from the time of the first ANC value < 0.5 x10^9/L until the time of the first ANC value after this where the ANC value was ≥ 0.5 x10^9/L.

ANC=absolute neutrophil count

End point type	Primary

End point timeframe:

Cycle 1.

End point values	Per Protocol - RGB-02 (Cycle 1)	Per Protocol - Neulasta® + RGB-02 (Cycle 1)	Full Analysis Set - RGB-02	Full Analysis Set - Neulasta® + RGB-02
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	112	111	121	117
Units: Days				
arithmetic mean (standard deviation)	1.7 (± 1.14)	1.6 (± 1.31)	1.8 (± 1.28)	1.7 (± 1.45)

Statistical analyses

Statistical analysis title	LS Mean difference (RGB-02 vs Neulasta®) for FAS

Statistical analysis description:

The estimated difference in mean duration of severe neutropenia between the 2 treatment arms and the 2-sided 95% CI for the difference between means were calculated using an analysis of covariance (ANCOVA) model with treatment, country, chemotherapy treatment setting (neoadjuvant or adjuvant), and baseline ANC value as factors in the model.

FAS = Full Analysis Set population

Comparison groups	Full Analysis Set - RGB-02 v Full Analysis Set - Neulasta® + RGB-02
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Least Squares mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.4

Notes:

[1] - If the upper limit of the 95% CI for the difference in means is ≤ 1 day and the lower bound of the 95% CI for the difference in means is ≥ -1 day, then the means in the 2 groups will be considered equivalent.

Statistical analysis title	LS Mean difference (RGB-02 vs Neulasta®) for PP

Statistical analysis description:

The estimated difference in mean duration of severe neutropenia between the 2 treatment arms and the 2-sided 95% CI for the difference between means were calculated using an analysis of covariance (ANCOVA) model with treatment, country, chemotherapy treatment setting (neoadjuvant or adjuvant), and baseline ANC value as factors in the model.

PP = Per Protocol population

Comparison groups	Per Protocol - RGB-02 (Cycle 1) v Per Protocol - Neulasta® + RGB-02 (Cycle 1)

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Least Squares mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.4

Notes:

[2] - If the upper limit of the 95% CI for the difference in means is ≤ 1 day and the lower bound of the 95% CI for the difference in means is ≥ -1 day, then the means in the 2 groups will be considered equivalent.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Safety population - RGB-02 (Cycle 1-2)
Reporting group description:	
All randomized subjects who received at least 1 dose of RGB-02 during Cycle 1 and 2 within RGB-02 arm.	
Reporting group title	Safety population - Neulasta® (Cycle 1-2)
Reporting group description:	
All randomized subjects who received at least 1 dose of Neulasta® during Cycle 1 and 2 within Neulasta® + RGB-02 arm.	

Serious adverse events	Safety population - RGB-02 (Cycle 1-2)	Safety population - Neulasta® (Cycle 1-2)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 121 (8.26%)	8 / 117 (6.84%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Lymphorrhoea			
subjects affected / exposed	2 / 121 (1.65%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	5 / 121 (4.13%)	6 / 117 (5.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 121 (0.00%)	2 / 117 (1.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenitis haemorrhagic			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 121 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety population - RGB-02 (Cycle 1-2)	Safety population - Neulasta® (Cycle 1-2)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 121 (80.17%)	109 / 117 (93.16%)	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 121 (4.96%)	9 / 117 (7.69%)	
occurrences (all)	6	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 121 (20.66%)	29 / 117 (24.79%)	
occurrences (all)	25	29	
Fatigue			
subjects affected / exposed	15 / 121 (12.40%)	18 / 117 (15.38%)	
occurrences (all)	15	18	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	13 / 121 (10.74%)	10 / 117 (8.55%)	
occurrences (all)	13	10	
Anaemia			
subjects affected / exposed	7 / 121 (5.79%)	6 / 117 (5.13%)	
occurrences (all)	7	6	
Neutropenia			
subjects affected / exposed	6 / 121 (4.96%)	6 / 117 (5.13%)	
occurrences (all)	6	6	
Febrile neutropenia			
subjects affected / exposed	5 / 121 (4.13%)	6 / 117 (5.13%)	
occurrences (all)	5	6	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	7 / 121 (5.79%)	6 / 117 (5.13%)	
occurrences (all)	7	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	53 / 121 (43.80%)	49 / 117 (41.88%)	
occurrences (all)	53	49	
Stomatitis			

subjects affected / exposed	15 / 121 (12.40%)	9 / 117 (7.69%)	
occurrences (all)	15	9	
Vomiting			
subjects affected / exposed	10 / 121 (8.26%)	11 / 117 (9.40%)	
occurrences (all)	10	11	
Constipation			
subjects affected / exposed	12 / 121 (9.92%)	4 / 117 (3.42%)	
occurrences (all)	12	4	
Diarrhoea			
subjects affected / exposed	25 / 121 (20.66%)	14 / 117 (11.97%)	
occurrences (all)	25	14	
Abdominal pain			
subjects affected / exposed	8 / 121 (6.61%)	2 / 117 (1.71%)	
occurrences (all)	8	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	75 / 121 (61.98%)	86 / 117 (73.50%)	
occurrences (all)	75	86	
Erythema			
subjects affected / exposed	8 / 121 (6.61%)	11 / 117 (9.40%)	
occurrences (all)	8	11	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	17 / 121 (14.05%)	24 / 117 (20.51%)	
occurrences (all)	17	24	
Arthralgia			
subjects affected / exposed	9 / 121 (7.44%)	11 / 117 (9.40%)	
occurrences (all)	9	11	
Myalgia			
subjects affected / exposed	6 / 121 (4.96%)	5 / 117 (4.27%)	
occurrences (all)	6	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 121 (7.44%)	7 / 117 (5.98%)	
occurrences (all)	9	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported