EU Risk Management Plan for Ryzneuta® (Efbemalenograstim alfa)

RMP version to be assessed as part of this application:

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QPPV name: José Alberto Ayala Ortiz

QPPV signature: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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Abbreviations

ADA	Anti-drug antibody
AML	Acute myeloid leukaemia
ARDS	Acute respiratory distress syndrome
CHO	Chinese hamster ovary
CLS	Capillary leak syndrome
CY	Cyclophosphamide
DLP	Data Lock Point
FN	Febrile Neutropenia
G-CSF	Granulocyte-colony stimulating factor
HL	Hodgkin lymphoma
IC	Immune complex
ICSR	Individual Case Safety Report
IL	Interleukin
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic syndrome
Mg	milligram
mL	millilitre
NHL	Non-Hodgkin lymphoma
PL	Patient Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
rhG-CSF	Recombinant human G-CSF
RMP	Risk Management Plan
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
US	United States

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Efbemalenograstim alfa
Pharmacotherapeutic group(s) (ATC Code)	ATC Code: NA Pharmacotherapeutic group: immunostimulants, colony stimulating factor;
Marketing Authorisation <Holder> <Applicant>	Evive Biotechnology Ireland Limited
Medicinal products to which this RMP refers	Ryzneuta 20 mg Solution for Injection (F-627)
Invented name(s) in the European Economic Area (EEA)	Ryzneuta
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Human granulocyte-colony stimulating factor (G-CSF) is a glycoprotein which regulates the production and release of neutrophils from the bone marrow. Efbemalenograstim alfa is a recombinant fusion protein containing G-CSF (rhG-CSF), fused to the Fc fragment of human immunoglobulin G2 (IgG2) with a 16 amino-acid linker. In solution, efbemalenograstim alfa forms homodimers via disulfide bonds between two the Fc moiety units. Efbemalenograstim alfa is a sustained duration form of G-CSF due to decreased renal clearance.
	Summary of mode of action: • Efbemalenograstim alfa and other rhG-CSFs have identical modes of action, namely binding to the G-CSF receptor on precursor cells in the bone marrow. This leads to proliferation and differentiation of granulocytes, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.
	Important information about its composition:

	Efbemalenograstim alfa is a recombinant fusion protein expressed in Chinese hamster ovary (CHO) cells containing G-CSF, fused to an IgG2 Fc fragment with a 16 amino-acid linker.
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	Proposed: Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).
Dosage in the EEA	Proposed: One 20 mg dose (a single pre-filled syringe) of Ryzneuta is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.
Pharmaceutical form(s) and strengths	Proposed: Pre-filled syringe contains 20 mg of efbemalenograstim alfa in 1 mL solution for injection. The concentration is 20 mg/mL.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

Ryzneuta is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Incidence and Prevalence:

Neutropenia and its complications, including febrile neutropenia (FN) and infection, remain major toxicities associated with myelosuppressive systemic cancer chemotherapy. In a US prospective cohort study, first-cycle febrile neutropenia occurred in 6% of adults with solid tumours being treated with myelosuppressive chemotherapy. Among patients with metastatic solid tumours, incidence of febrile neutropenia during myelosuppressive chemotherapy ranged from 13% to 21% in a large retrospective study. [1]

The incidence of FN for the most frequently used breast cancer regimens in European practice was 6%. However, grade 4 neutropenia occurred in a high proportion of patients (34%) and significantly impacted chemotherapy delivery. [2] The reported incidence of chemotherapy-induced neutropenia varies widely between 6–50% of patients depending on the cancer type, disease staging, patient functional status, and chemotherapy regimen. [3]

The FN risk of patients treated with anthracycline-based regimens was <10%. Over 20% of non-Hodgkin lymphoma (NHL) patients and 15% of Hodgkin lymphoma (HL) patients developed FN at some point during the course of their chemotherapy treatment. Many lymphoma patients (54% of NHL and 40% of HL patients) also experienced grade 4 neutropenia, which was associated with delays in planned chemotherapy treatment. [2]

Demographics of the population:

All patients who are treated with chemotherapy are at risk for the development of neutropenic complications. Some patients are at greatest risk. Identified risk factors for neutropenia can be classified as patient-specific or regimen-specific.

Patients with hematologic malignancies are at greater risk for neutropenia than patients with solid tumours because of the underlying disease process as well as the intensity of the treatment that is required.[4]
The risk of neutropenia also has been related to the phase of therapy; the greatest risk is in the earliest cycles.[4]

Age is a risk factor for the development of severe neutropenia or FN, and it also may be associated with other patient characteristics that affect that risk. In some studies, it has been found that poor performance status (e.g., World Health Organization Grade > 1), as a measure of fragility, is a significant risk factor. Thus, a patient's physiologic age, rather than chronologic age, may be a more accurate predictor of the neutropenic risk.
Another patient-specific risk factor for later neutropenic complications is the patient's early hematologic response to chemotherapy. This has the advantage of being a functional assessment of the effect of treatment on the patient's bone marrow. The first cycles of treatment can show which patients are at risk, after which dose modifications or prophylactic growth factors are often used, thus reducing the risk in later cycles. Studies have shown the predictive value of the first-cycle nadir in leukocyte counts and decreases in haemoglobin levels for predicting neutropenic complications in later cycles. [4]

Most studies did not evaluate or report significant associations of neutropenic complications with patient gender. [5] Ethnicity was not identified as risk factor for developing severe neutropenia.

The chemotherapy regimen the primary determinants of the risk of neutropenia, and some regimens are more myelotoxic than others. For example, combined cyclophosphamide, methotrexate, and 5-fluorouracil is less toxic than doxorubicin and cyclophosphamide or combined cyclophosphamide, doxorubicin, and 5-fluorouracil.[4]

The main existing treatment options:
Management of severe neutropenia in cancer patients receiving myelotoxic chemotherapy remains a challenge in clinical practice since it can result in significant morbidity and/or mortality due to infectious complications, as well as chemotherapy dose reductions/delays, which may compromise treatment outcomes for cancer patients. [1, 6]
For instance, poor outcome in cancer patients has been attributed to failure to deliver planned chemotherapy regimens for lymphoma, breast cancer, lung cancer and ovarian cancer.[7] Chemotherapy dose reductions and dose delays, as a result of Chemotherapy-induced neutropenia and FN, can lead to reduced patient survival.[2] Prevention of chemotherapy-induced FN is, therefore, a clinical priority for patients undergoing treatment for solid tumours and lymphoma. [7]

Supportive care with recombinant human G-CSFs (rhG-CSFs) has been very beneficial in reducing neutropenia and its complications in patients receiving myelotoxic chemotherapy. [1]

The level of in-hospital mortality associated with patients who are hospitalised for FN is 9.5% on average and more than 21% for patients with co-morbidities [2].

Recombinant human G-CSF products such as filgrastim, lenograstim, lipegfilgrastim, and pegfilgrastim are able to stimulate neutrophil production and have been approved in the US and/or EU for the management of

neutropenia in cancer patients receiving myelotoxic chemotherapy. Filgrastim and lenograstim, which are cleared by excretion by kidney and by G-CSF receptor-mediated endocytosis, have relatively short half-lives, and require daily dosing post chemotherapy. Pegfilgrastim and lipegfilgrastim are long-acting rhG-CSF that are comprised of filgrastim covalently linked to a 20kD polyethylene glycol (PEG) molecule. Addition of PEG molecule prevents rapid renal clearance of the drug and allows for dosing once per chemotherapy cycle.

Efbemalenograstim alfa (F-627) was designed to have a similar mechanism of action as other G-CSF class products such as filgrastim, lenograstim, lipegfilgrastim, and pegfilgrastim, and to have a half-life sufficient to allow for once-per-cycle dosing, similar to pegfilgrastim and lipegfilgrastim. In that respect, F-627 represents a non-pegylated alternative to pegfilgrastim and lipegfilgrastim.

Natural history of the indicated condition in the population, including mortality and morbidity:
Neutropenia is a well-recognized condition that predisposes patients to bacterial and fungal infection; susceptibility to infection increases dramatically with severe neutropenia (ANC<0.5 × 10^9/L).

Cytotoxic chemotherapy agents target rapidly dividing cells, including myeloid progenitor cells; therefore, patients with malignancies receiving chemotherapy are at risk of developing neutropenia. The degree of risk, as reflected by the incidence and duration of severe neutropenia, and the rate of FN (i.e., severe neutropenia with a coexistent fever), are substantially driven by the chemotherapy agents and doses used. Other patient-related factors, such as age, prior therapy, other co-morbidities, and the occurrence of neutropenia and/or FN in prior chemotherapy cycles may also result in patients being considered at high-risk of developing FN.
Due to the risk of death from rapidly spreading infection, cases of FN are typically treated aggressively, with administration of broad-spectrum IV antibiotics and hospitalization in high-risk patients.

Reported studies from literature illustrate the impact of FN occurrence on hospitalisation and mortality, showing inpatient mortality rates of 9.5–12.5%. [7] The occurrence of severe neutropenia or FN following chemotherapy, as well as persistent neutropenia at the scheduled time of subsequent chemotherapy administration, even if moderate in severity, are also reasons for oncologists to delay further chemotherapy or provide it at a reduced dose, potentially impacting its effectiveness.

The risk of neutropenic complications including febrile neutropenia increases in direct proportion to the severity and duration of neutropenia.

Management of severe neutropenia in cancer patients receiving myelotoxic chemotherapy remains a challenge in clinical practice since it can result in significant morbidity and/or mortality due to infectious complications, as well as chemotherapy dose reductions/delays, which may compromise treatment outcomes for cancer patients.

Important co-morbidities:

The presence of comorbidity affects the care of cancer patients, many of whom are living with multiple comorbidities.

Comorbidity refers to the existence of a long-term health condition in the presence of a primary disease of interest. Having one or more comorbidities may influence the patient's prognosis for a primary disease such as cancer. Comorbidity may influence the timing of cancer diagnosis, in either a positive or a negative way. [8]

Chronic comorbidities can also influence the risk of FN. [9]

History of several comorbidities, including bone marrow suppression (pre-existing anaemia, thrombocytopenia, and/or neutropenia), COPD, CHF, HIV infection/AIDS, liver disease, peptic ulcer disease, renal disease, autoimmune disease, and thyroid disorder may increase the risk of developing FN or severe neutropenia in patients treated with chemotherapy.

In addition to individual comorbidities, total number of comorbidities was significantly associated with FN risk.

These results may assist FN risk stratification for cancer patients and should be considered when making decisions regarding treatment choices and the use of prophylactic G-CSF. [9]

Part II: Module SII - Non-clinical part of the safety specification

Efbemalenograstim alfa is a highly innovative recombinant fusion protein consisting of human G-CSF and human IgG2 Fc fragments and intended to treat chemotherapy-induced neutropenia in cancer patients. Unlike the currently marketed forms of rhG-CSF, efbemalenograstim alfa is produced in CHO cells. Efbemalenograstim alfa naturally exists as a homodimer of two G-CSF-IgG2 molecules. Efbemalenograstim alfa has the same mechanism of action as other rhG-CSF products including filgrastim, lenograstim, lipegfilgrastim, and pegfilgrastim to simulate neutrophil proliferation. However, the pharmacokinetics of efbemalenograstim alfa is significantly different from the existing short-acting G-CSF products due to the fact that the uniquely engineered IgG2 Fc moiety not only increases the molecule size to evade renal clearance, but it also interacts with neonatal receptors (FcRn) on cell surface to further extend its half-life.

The bioactivity of efbemalenograstim alfa *in vitro* was evaluated in comparison with filgrastim and pegfilgrastim. Efbemalenograstim alfa activated STAT3 in cell lines, including M-NFS-60, and 32D-G-CSFR cell lines expressing G-CSFR. STAT3 activation is a down-stream event resulting from the interaction of G-CSF ligand and G-CSFR and G-CSFR activation. Efbemalenograstim alfa was able to stimulate the proliferation of M-NFS-60 cells in a dose-dependent manner. The proliferation of M-NFS-60 stimulated by efbemalenograstim alfa was blocked in the presence of anti-hG-CSF mAB.

The *in vivo* activity of efbemalenograstim alfa was evaluated in healthy animals and experimental neutropenia animal models.

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity use

- Key issues identified from acute or repeat-dose toxicity studies

At higher doses, the acute toxicity studies in rats and monkeys showed that the findings were exaggerated pharmacological effects of G-CSF. No adverse findings were noted in the safety pharmacology and local tolerance studies.

Three-month toxicity studies with weekly subcutaneous injection and one-month recovery were conducted in rats and monkeys. The major toxicities of efbemalenograstim alfa observed were increased WBC and neutrophils, spleen enlargement, and infiltration of neutrophils in organs; all thought to be due to the exaggerated pharmacologic effects of G-CSF at high doses. Rear limb weakness and swelling were also observed. Evidence of limb weakness after repeated dosing has been reported with other similar rhG-CSF pharmacological agents and is thought to be the sequelae of high-dose pharmacology and fluid retention, which may manifest as tissue oedema.

In the 6-month rat toxicity study, adverse effects secondary to exaggerated pharmacology were observed. These adverse effects included limited rear limb usage and tissue swelling. Because of the ethical reasons and high stress to animals, the protocol was modified with the reduction in dose and extension of the dosing interval. As expected from the exaggerated pharmacology, the leucocytosis, anaemia, and extramedullary haematopoiesis were observed; however, histopathology did not show chronic inflammation.

- Reproductive/developmental toxicity
  - A 6-month rat study, fertility, embryofoetal studies in rats and rabbits, and a pre-/postnatal study were also performed.
  - Fertility, embryofoetal, and pre- and postnatal studies in rats revealed no adverse effects on developing foetuses or reproductive performance in rats or rabbits (embryofoetal only).
- Genotoxicity: Genotoxicity studies have not been conducted
- Carcinogenicity: Carcinogenicity studies have not been conducted

Safety pharmacology

Safety studies for efbemalenograstim alfa included single-dose acute toxicity studies in rats and Cynomolgus monkeys; safety pharmacology studies in mice including an *in vitro* hERG binding study; local tolerance tests including blood vessel irritation and muscle irritation in rabbits, the allergic response in guinea pigs, and *in vitro* haemolytic tests. Less than 15% inhibition of the hERG channel was identified at concentrations up to 1000 ng/mL, indicating no meaningful interaction with this ion channel.

Summary of non-clinical part of the safety specification

In conclusion, the preclinical studies for efbemalenograstim alfa demonstrated that the investigational fusion protein is similar or superior to many approved G-CSF therapies, including filgrastim, lenograstim, and pegfilgrastim. The data presented clearly show that many desirable pharmacological effects of efbemalenograstim alfa, including STAT3 activation, and cell proliferation both in normal animals and neutropenic animal models are identical to those observed in preclinical studies of marketed rhG-CSF therapies. It is worth noting that in the CY-induced neutropenia monkey model, neutrophil recovery and decrease of severity of neutropenia in the efbemalenograstim alfa group are comparable to, if not slightly better than these from rhG-CSF and pegfilgrastim-treated monkeys. Similar to other rhG-CSF drugs, efbemalenograstim alfa exhibited nonlinear pharmacokinetics in rats and monkeys. C_{max} and AUC increased more than proportional to the increase of efbemalenograstim alfa dose. A correlation of PK/PD responses was demonstrated in the pharmacology studies. The observed toxicities of efbemalenograstim alfa were exaggerated G-CSF pharmacology and included increased WBC and neutrophils, enlarged spleens, and infiltration of neutrophils in specific organs. Preclinical studies fully supported the clinical development of efbemalenograstim alfa.

Part II: Module SIII - Clinical trial exposure

Brief overview of development

An overview of the clinical development program for efbemalenograstim alfa (formerly F-627) is presented below. A total of 10 clinical studies have been completed in over 1200 subjects. No studies are ongoing. The clinical studies include:

- Three adequate and well-controlled Phase III studies, which were randomized, parallel group, multicentre studies in females with breast cancer receiving myelotoxic chemotherapy. Study GC-627-04 established the efficacy and safety of F-627, compared to placebo, in reducing the duration of neutropenia and the incidence of FN, while Studies GC-627-05 and SP11631 compared the efficacy and safety of F-627 to pegfilgrastim and filgrastim, respectively, with a primary goal of demonstrating non-inferiority of F-627 to those marketed rhG-CSFs with respect to duration of neutropenia;
- Two Phase II dose-ranging studies (Studies GC-627-02 and SP-CDR-1-1302) in females with breast cancer;
- Three Phase I studies evaluating safety and pharmacokinetics (PK)/pharmacodynamics (PD) in females with breast cancer (Studies 2012-F-627-CH1, SP-CDR-1-1301, and SP11502); and
- Two Phase I studies in healthy male volunteers to assess initial PK/PD and safety/tolerability (Study GC-F-627-01) and to compare lyophilized and liquid F-627 formulations (Study GC-F-627-03).

A total of 734 breast cancer patients were administered F-627 subcutaneously (SC) at weight-based doses of 80, 240, or 320 µg/kg/dose or as fixed doses of 10 or 20 mg, for up to 6 repeat doses (once per chemotherapy cycle). Depending on the study, these patients received 1 of the following 5 chemotherapy regimens:

- EC: 100 mg/m^2 epirubicin + 600 mg/m^2 cyclophosphamide
- TA: 75 mg/m^2 Taxotere® (docetaxel) + 60 mg/m^2 Adriamycin® (doxorubicin)
- TAC [500]: 75 mg/m^2 docetaxel + 50 mg/m^2 doxorubicin + 500 mg/m^2 cyclophosphamide

  TAC [600]: 75 mg/m^2 docetaxel + 50 mg/m^2 doxorubicin + 600 mg/m^2 cyclophosphamide
- TC: 75 mg/m^2 docetaxel + 600 mg/m^2 cyclophosphamide

Most studies included 4 cycles of chemotherapy; SP-CDR-1-1301 and SP11502 included 6 cycles. All cycles of chemotherapy were 21 days in length.

A total of 54 healthy volunteers (all male) were administered F-627 at single SC doses ranging from 30 to 360 µg/kg/dose, or as a 20 mg fixed dose.

With respect to geography, 3 studies were performed in the US and Europe (GC-627-02, GC-627-04, and GC-627-05), and 5 studies were conducted in China (2012-F-627-CH1, SP-CDR-1-1301, SP-CDR-1-1302, SP11502, and SP11631). The healthy volunteer studies (GC-F-627-01 and GC-F-627-03) were conducted in Australia.

There were two efbemalenograstim alfa formulations used in the clinical development program: a lyophilized formulation and a liquid formulation in a prefilled syringe（PFS. The PFS was used in the Phase III studies with fixed dosing of 20 mg; this is the formulation intended for marketing. The lyophilized formulation alone was used in the two Phase II studies and four Phase I studies. A Phase I PK/PD comparison study (GC-F-627-03) evaluated both formulations in healthy volunteers.

A unique administration of efbemalenograstim alfa on the same day as adjuvant chemotherapy was used in study SP11502; all other studies in the clinical program dosed efbemalenograstim alfa at least 24 hours after chemotherapy administration. Dosing on the same day as chemotherapy is not recommended for any rhG-CSF product due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy. For that reason, results from the 7 patients enrolled in Study SP11502 were not included in safety and efficacy analyses.

Table SIII.1: Duration of exposure

Duration of exposure	Patients
<1 m	54
1 to <3 m	712
3 to <6 m	15
≥6 m etc.	0
Total	781*

*7 patients with cancer in study SP11502 were excluded due to administration of efbemalenograstim alfa on the same day as adjuvant chemotherapy.

Table SIII.2: Age group and gender

Age group	Patients	
	M	F
Adults (18-64)	54	671
Elderly people		
65-74 years	0	53
75-84 years	0	3
85+ years	0	0
Total	54	727*

*7 patients with cancer in study SP11502 were excluded due to administration of efbemalenograstim alfa on the same day as adjuvant chemotherapy.

Table SIII.3: Dose of Exposure with Efbemalenograstim alfa (F-627)

Type of Study	**Study Identifier**	**Objectives of the Study**	**Study Design and Type of Control**	**Dose Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Patients**	**Duration of Treatment**
Phase I	GC-F-627-01	Safety, PK, PD, dose escalation	Single centre, open-label, single dose, dose escalation study in healthy male subjects Location: Australia	F-627 30, 60, 120, 240 or 360 µg/kg [Lyo]/single dose on Day 1	30	Healthy subjects	Single dose
Phase I	GC-F-627-03	Safety, PK, PD between lyophilized formulation and liquid formulation in PFS	Single centre, randomized, active-controlled, open-label, single dose study in healthy male subjects Location: Australia	F-627 20 mg [PFS] or F-627 20 mg [Lyo]/single dose on Day 1	24	Healthy subjects	Single dose

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment
Phase I	2012-F-627-CH1	Safety, PK, PD	Single centre, open-label, multi-dose, dose escalation study of four 21-day cycles of treatment Location: China	F-627 80 µg/kg [Lyo]/dosed on cycle Day 3 for 4 cycles, F-627 240 µg/kg [Lyo]/dosed on cycle Day 3 for 4 cycles, F-627 320 µg/kg [Lyo]/dosed on cycle Day 3 for 4 cycles.	18	Patients (women postoperative breast cancer subjects receiving EC chemotherapy followed by paclitaxel or docetaxel and supportive care)	Multi-dose (four 21-day cycles of treatment)
Phase Ib	SP-CDR-1-1301	Safety, PK, PD	Multicentre, open-label, multi-dose, dose escalation study of six 21-day cycles of treatment Location: China	F-627 240 µg/kg [Lyo]/dosed on cycle Day 2 for 6 cycles, F-627 320 µg/kg [Lyo]/dosed on cycle Day 2 for 6 cycles.	15	Patients (Women with postoperative breast cancer subjects receiving adjuvant TAC [500] chemotherapy)	Multi-dose (six 21-day cycles of treatment)

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment
Phase Ib	SP11502	Safety, PK, PD	Single centre, open-label, multi-dose study of six 21-day cycles of treatment in female postoperative breast cancer subjects receiving adjuvant TAC [500] chemotherapy Location: China	F-627 320 µg/kg [Lyo]/dosed on cycle Day 1 for 6 cycles	7	Patients (women with breast cancer receiving TAC, same day dosing)	Multi-dose (six 21-day cycles of treatment)

Type of Study	**Study Identifier**	**Objectives of the Study**	**Study Design and Type of Control**	**Dose Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Patients**	**Duration of Treatment**
Phase II	GC-627-02	Safety/efficacy, dose finding; F-627 dose with body weight adjusted; proof of concept in comparison to pegfilgrastim.	Multicentre, randomized, multi-dose, open-label, active-controlled, non-inferiority study of four 21-day cycles of treatment. Locations: Russia, Ukraine, US	F-627 80 µg/kg [Lyo]/dosed on cycle Day 2 for 4 cycles (TC only), F-627 240 µg/kg [Lyo]/dosed on cycle Day 2 for 4 cycles, F-627 320 µg/kg [Lyo]/dosed on cycle Day 2 for 4 cycles, Pegfilgrastim (Neulasta®) 6mg/dosed on cycle Day 2 for 4 cycles.	232	Patients, females with Stage I-IV breast cancer receiving concurrent TC or TAC [600] chemotherapy	Multi-dose (four 21-day cycles of treatment)

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment
Phase II	SP-CDR-1-1302	Safety/efficacy, dose finding; F-627 fixed dose; proof of concept in comparison to filgrastim	Multicentre, randomized, open-label, multi-dose, active-controlled, non-inferiority study of four 21-day cycles of treatment Location: China	F-627 20 mg [Lyo]/dosed on cycle Day 3 for 4 cycles, F-627 10 mg [Lyo]/dosed on cycle Day 3) for 4 cycles, Filgrastim (GRAN®) 5µg/kg/day/dosed on cycle Day 3 + daily up to 2 weeks for 4 cycles.	130	Patients, postoperative breast cancer females receiving concurrent EC chemotherapy	Multi-dose (four 21-day cycles of treatment)

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment
Phase III	GC-627-04	Safety/efficacy; F-627 fixed dose in comparison to placebo	Multicentre, randomized F-627 placebo (2:1), multi-dose, double-blind, placebo-controlled, superiority study of four 21-day cycles of F-627 treatment Locations: Hungary, Russia, Ukraine, US	F-627 20 mg [PFS]/dosed on cycle Day 2 for 4 cycles, Placebo/dosed on cycle Day 2 for 1 cycle + F-627 20 mg [PFS]/dosed on cycle Day 2 for 3 cycles.	122	Patients, females with Stage II-IV breast cancer receiving concurrent TA chemotherapy	Multi-dose (four 21-day cycles of treatment)

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Dose Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Patients	Duration of Treatment
Phase III	GC-627-05	Safety/efficacy; F-627 fixed dose in comparison to pegfilgrastim	Multicentre, randomized, multi-dose, open-label, active controlled, non-inferiority study of four 21-day cycles of F-627 or Neulasta treatment plus 6-month follow-up. Locations: Bulgaria, Hungary, Russia, Ukraine, US	F-627 20 mg [PFS]/dosed on cycle Day 2 for 4 cycles, Pegfilgrastim (Neulasta®) 6 mg/dosed on cycle Day 2 for 4 cycles.	393	Patients, females with Stage I- III breast cancer receiving concurrent TC chemotherapy	Multi- dose (four 21-day cycles of treatment plus 6-month follow-up)
Phase III	SP11631	Efficacy/safety; F-627 fixed dose in comparison to filgrastim daily administration.	Multicentre, randomized, open-label, multi-dose, active controlled, non-inferiority study of four 21-day cycles of F-627 or GRAN treatment. Location: China	F-627 20 mg [PFS]/dosed on cycle Day 3 for 4 cycles, Filgrastim (GRAN®) 5 µg/kg/day/dosed on cycle Day 3 + daily up to 2 weeks for 4 cycles.	239	Patients, females with breast cancer receiving concurrent EC chemotherapy	Multi-dose (four 21-day cycles of treatment)

Abbreviations: EC = epirubicin 100 mg/m^2 + cyclophosphamide 600 mg/m^2; Lyo = lyophilized formulation; PD = pharmacodynamic; PFS = liquid form pre-filled syringe; PK = pharmacokinetic; TA =docetaxel 75 mg/m^2 + doxorubicin 60 mg/m^2; TAC[500] = docetaxel 75 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 chemotherapy; TAC[600] = docetaxel 75 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 600 mg/m^2 chemotherapy; TC = docetaxel 75 mg/m^2 + cyclophosphamide
600 mg/m^2; US = United States of America
N is the number of treated subjects in the study.

Table SIII.4: Ethnic origin

Ethnic origin	Healthy Volunteers or Patients
White	526
Black	3
Hispanic	0
Asian	250
Other	2
Total	781*

*7 patients with cancer in study SP11502 were excluded due to administration of efbemalenograstim alfa on the same day as adjuvant chemotherapy.

Part II: Module SIV - Populations not studied in clinical trials

Efbemalenograstim alfa is intended for use in the same populations as those of approved rhG-CSF products and in particular long acting rhG-CSF products. The sought indicated population is adult patients treated with cytotoxic chemotherapy for malignancy.

Paediatric

The efbemalenograstim alfa development program benefited from advice and guidance received from the US Food and Drug Administration (FDA) at various time points during development, including a 29 Dec 2016 agreement on an initial Paediatric Study Plan (iPSP), and an agreement on deferral of paediatric studies/assessment until after BLA approval (iPSP Agreement Letter 29 Dec 2016).

In addition to FDA's development guidance, scientific advice was sought in 2018 from the United Kingdom Medicines & Healthcare products Regulatory Agency (MHRA) and the Medicines Evaluation Board (MEB) in the Netherlands. These authorities expressed general agreement that the efbemalenograstim alfa nonclinical development program and clinical development program (in particular, the Phase III study designs and immunogenicity testing plans) were sufficient to support Medicines Authorisation Application (MAA) filing. On 04 Sep 2020, agreement was reached with the European Medicines Agency (EMA) on a Paediatric Investigation Plan and deferral for efbemalenograstim alfa.

Pregnant and breastfeeding women

No studies of efbemalenograstim alfa have been conducted in pregnant women. Patients pregnant or having the intention to become pregnant during the study were excluded from clinical trials. No pregnancies occurred and no women were breast-feeding in the clinical development program.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

1. Patients <18 years of age
   a. Reason for exclusion: There are no data available on the pharmacokinetics of efbemalenograstim alfa in children.
   b. Is it considered to be included as missing information? Yes.
   c. Rationale: The safety and efficacy of Ryzneuta in children has not yet been established and no recommendation on a posology can be made.
2. Patients with radiation therapy within 4 weeks prior to enrolment
   a. Reason for exclusion: To avoid agents with potential to confound assessment of immunologic endpoints.
   b. Is it considered to be included as missing information? No.
   c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.
3. Pregnancy and Lactation

a. Reason for exclusion: It is not known if efbemalenograstim alfa is secreted in breast milk and there are no data from the use of efbemalenograstim alfa in pregnant women, although animal studies have not shown reproductive toxicity.

   A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from efbemalenograstim alfa therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

b. Is it considered to be included as missing information? Yes.

c. Rationale: No recommendation can be made given the lack of data in pregnant and lactating women.

4. Patients with history of alcohol or drug abuse

   a. Reason for exclusion: History of alcohol or drug abuse that may affect the compliance with the study.

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

5. Patients with known allergy to granulocyte colony stimulating factor (G-CSF) or excipients

   a. Reason for exclusion: Contraindicated in case of previous allergy or hypersensitivity to the active substance or to the excipients.

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

6. Patients with diseases or symptoms unsuitable for participating in the clinical trial based on the investigator's judgment

   a. Reason for exclusion: the study drug may compromise the health of the patient or the assessment of AEs may be affected.

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

7. Patients with breast cancer who have received neoadjuvant chemotherapy before surgery

   a. Reason for exclusion: The objective of excluding patients with neoadjuvant chemotherapy before surgery is to avoid confounding factors.

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

8. Patients with prior bone marrow or stem cell transplant

   a. Reason for exclusion: Exclusion for patient safety, to minimize the development of treatment-related myelodysplastic syndrome (t-MDS)/acute myeloid leukaemia (AML).

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

9. Patients with other malignant tumours other than breast cancer

   a. Reason for exclusion: Patients are excluded to avoid or minimize confounding factors.

   b. Is it considered to be included as missing information? No.

   c. Rationale: Exclusion not relevant for routine medical practice.

10. Patients who have received treatment with rhG-CSF within six (6) weeks prior to randomization

a. Reason for exclusion: Patients are excluded to avoid confounding factors that may lead to uninterpretable data.
b. Is it considered to be included as missing information? No.
c. Rationale: Exclusion not relevant for routine medical practice.

11. Patients diagnosed with acute cardiac failure congestive, cardiomyopathy, or myocardial infarction by clinical diagnosis, ECG, or other approaches
a. Reason for exclusion: Exclusion for patient safety: The objective was to exclude patients who had a cardiac event and or hospitalization six months before randomization as patients are likely to be unstable in health condition.
b. Is it considered to be included as missing information? No.
c. Rationale: Exclusion not relevant for routine medical practice.

12. Patients with any disease that may cause splenomegaly
a. Reason for exclusion: Exclusion for patient safety-because G-CSF can cause splenomegaly and splenic rupture. Patients with diseases that increase the risk of splenomegaly are excluded.
b. Is it considered to be included as missing information? No.
c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.

13. Patients with acute infection, chronic active hepatitis B within one (1) year (unless patients tested negative for HBsAg prior to enrolment), or Hepatitis C
a. Reason for exclusion: Exclusion is based on patient safety and confounding factors. Neutropenia frequently occurs in patients with chronic hepatitis B infection. To avoid confounding and difficulty interpreting the data emanating from the trial, patients are excluded.
b. Is it considered to be included as missing information? No.
c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.

14. Patients with known human immunodeficiency virus (HIV) positive or AIDS
a. Reason for exclusion: Exclusion is based on patient safety and confounding factors: Neutropenia frequently occurs in patients with Human immunodeficiency virus (HIV) infection/AIDS. To avoid confounding and difficulty interpreting the data emanating from the trial, patients are excluded.
b. Is it considered to be included as missing information? No.
c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.

15. Patients with active tuberculosis (TB); history of TB exposure, unless negative for tuberculin test
a. Reason for exclusion: Exclusion for patient safety/confounding factors: Neutropenia is a complication of TB and anti-tuberculous therapy; to avoid confounding and difficulty interpreting the data emanating from the trial, patients are excluded.
b. Is it considered to be included as missing information? No.

c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.

16. TB patients undergoing treatment; or suspected TB evaluated by chest x-ray
    a. Reason for exclusion: Neutropenia is a rare complication of anti-tuberculous therapy; to avoid confounding and difficulty interpreting the data emanating from the trial, patients are excluded.
    b. Is it considered to be included as missing information? No.
    c. Rationale: No difference in safety profile is expected in these patients therefore it is not included as missing information.
17. Patients with sickle-cell anaemia
    a. Reason for exclusion: Patient safety – patients with sickle cell disease or trait are at risk of developing sickle cell crisis, splenomegaly/splenic rupture. Caution should be taken when giving any G-CSF to patients with sickle cell disease or trait.
    b. Is it considered to be included as missing information? No.
    c. Rationale: Sickle cell crisis in patients with sickle cell disease is included as a potential risk in the RMP.
18. Patients who have received any other study drugs within one (1) month or five (5) half-lives of the other study drugs prior to enrolment (whichever is longer)
    a. Reason for exclusion: For patient safety and GCP, patients can only enrol in one therapeutical clinical trial at a time; this is also to avoid confounding in the interpretation of safety and efficacy data.
    b. Is it considered to be included as missing information? No.
    c. Rationale: Exclusion not relevant for routine medical practice.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency, or those caused by prolonged exposure due to limited population numbers studied. Given that F-627 is a rhG-CSF product with similarities to other rhG-CSF products including pegylated rhG-CSF, pre-existing information on the potential nature and frequency of adverse reactions could inform upon the possible expected safety profile of F-627.

Patients (n=393) included in Study GC-627-05, a Phase III, Randomized, Multi-Centre, Open-Label, Active-Controlled Clinical Trial in Women with Breast Cancer Receiving either fixed dose F-627 or Neulasta, also returned for a follow-up visit 6 months post final study drug administration for assessment of the subject's disease progression/survival status, as well as additional chemotherapy and rhG-CSF usage.

The 6-month follow-up visit was completed by 363 (92.4%) subjects. Most of the subjects were reported to have attained stable disease status by the 6-month follow-up, including 112 (56.9%) subjects who received F-627 and 101 (51.5%) of subjects who received Neulasta®. Of these 213 subjects, 4 subjects randomized to F-627 subsequently experienced disease progression. There were 2 deaths in the Neulasta® arm occurred

during the 6-month follow-up; one was due to peritonitis while the other one was due to worsening of underlying condition. There were 69 (35.0%) subjects treated with F-627 and 79 (40.3%) subjects treated with Neulasta® who were not considered to have attained stable disease status at the 6-month follow-up period. Only a small proportion of subjects (4.6%; in both treatment groups) received additional G-CSF as part of their ongoing treatment after EOT.

The majority of subjects did not have any clinically significant vital sign abnormalities noted (i.e., values lower or higher than reference ranges). Overall, 11 subjects had clinically significant abnormalities, as assessed by the Investigator in vital sign results observed during the study; however, at the 6-month follow-up visit, no vital sign results, including the 11 subjects were deemed clinically significant abnormalities.

A total of 734 patients have been exposed to efbemalenograstim alfa in company-sponsored Phase 1 to 3 clinical trials.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Paediatric population	Not included in the clinical development program, deferred to post approval
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not included in the clinical development program Ethnicity has not been shown to be a factor in the safety of G-CSF products
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program Genetic polymorphisms have not been shown to be a factor in the safety of G-CSF products

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable. Ryzneuta is neither authorised nor commercialised in any country in the world.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Ryzneuta is not structurally or pharmacologically related to any drug known to cause abuse or dependence. The product PK and PD characteristics do not suggest any potential effect on CNS that may produce drug dependence. During the clinical development program there have been no AEs that would be indicative of abuse or a dependence potential and no behaviour or withdrawal symptoms were observed after stopping treatment.

Ryzneuta is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are not considered important for inclusion in the list of safety concerns:

- Hypersensitivity
- Bone pain
- Pulmonary oedema
- Leucocytosis
- Capillary leak syndrome
- Sickle cell crisis in patients with sickle cell disease
- Glomerulonephritis
- Acute respiratory distress syndrome
- Severe splenomegaly/splenic rupture
- Aortitis
- Malignant cell growth, MDS and AML

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Bone pain

  Bone pain was the most frequently reported adverse reaction in clinical trials. It was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

- Leucocytosis

  All reported cases with leucocytosis during clinical trials were non-serious in nature.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting:

- Hypersensitivity

  The risk of hypersensitivity is not included as an important identified risk, considering that it is well characterised and addressed via SmPC sections 4.3, 4.4 and 4.8, and package leaflet section 2. This is also in line with the safety concerns of other class products.

- Pulmonary oedema, capillary leak syndrome, sickle cell crisis in patients with sickle cell disease, glomerulonephritis, acute respiratory distress syndrome, severe splenomegaly/splenic rupture, aortitis, malignant cell growth, MDS and AML

  These risks are known risks of the class products [10,11,12,13]. They are adequately addressed in section 4.4. and 4.8 of the SmPC and there is no need for further characterization (there is no additional pharmacovigilance plan or risk minimisation measures in place). With the exception of asymptomatic splenomegaly, none of the above-mentioned adverse reactions were reported in clinical studies with efbemalenograstim alfa.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Considering data from clinical trials, no risks are considered important identified risks for inclusion in the list of safety concerns in the RMP. Immunogenicity is the only important potential risk. However, all risks can be adequately managed via product information and no risks require further pharmacovigilance activities beyond adverse reaction reporting and signal detection.

Important Potential Risk 1: Immunogenicity

Immunogenicity was reported with other G-CSFs. All therapeutic proteins have potential for immunogenicity. Anti-F-627 binding antibodies were detected in 30 (15.2%) subjects treated with F-627 in a phase III clinical trial. 17 (8.6%) subjects had treatment-emergent binding anti-F-627 antibodies in F-627 arm. No neutralizing antibodies to F-627 or G-CSF were detected in any subject treated with F-627 at any time point. The risk can be adequately managed by appropriate risk minimisation activities in the product information; hence the risk-benefit impact is acceptable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks:

Not applicable.

Important Potential Risks:

Potential risk – Immunogenicity	
Frequency with 95 % CI	Unknown
Seriousness/outcome	The outcome of immune responses to therapeutic biologics can range from no apparent effect to serious adverse events, including life-threatening complications such as anaphylaxis, neutralization of the effectiveness, or neutralization of endogenous proteins with nonredundant functions.
Severity and nature of risk	Immune response to therapeutic biologics may result in changes in bioavailability, safety, efficacy, pharmacokinetics including potential cross-reactivity to endogenous proteins, inhibition of the function of endogenous protein, injection-site reactions, systemic reactions, formation of anti-drug antibodies (ADA), neutralizing antibodies, immune complexes (ICs) or anti-idiotypic antibodies. Therefore, the severity depends on the specific immune response affected by both patient-related and product-related factors.
Background incidence/prevalence	Virtually all therapeutic proteins elicit an immune response with the consequent production of ADA. [14] Of the 438 subjects that received F-627 in Phase III studies, 20 subjects (4.6%) developed treatment-emergent ADA to F-627. 13 out of 436 subjects (3.7%) developed treatment-emergent ADA to the G-CSF. There were no neutralizing ADAs to F-627 or G-CSF in these subjects per cell-based proliferation assays using either F-627 or G-CSF as a stimulant.
Risk factors and risk groups	In general, the immunogenicity of therapeutic proteins can be influenced by many factors, including the genetic background of the patient, the type of disease, the type of protein, the presence of conjugates or fragments, the route of administration, dose frequency, and duration of treatment. [15]
Potential Mechanism	The presence of ADAs may be associated with reduced clinical efficacy through two main mechanisms. ADAs that

	compete with the cytokine binding site have neutralising properties as they block the pharmacological function of the drug. ADAs directed against the Fc fragment lead to formation of ICs associated with enhanced drug clearance that may also influence the clinical response to biologic treatment through leading to sub-therapeutic drug levels. [16] Most adverse effects consequential to ADA formation are a consequence of formation of ICs between the ADA and therapeutic protein. [17] Subcutaneous administration has unique immunogenicity challenges for some products compared to intravenous administration that are likely due to differences in immune system exposure and antigen presentation mechanisms. [18]
Preventability	Unknown
Impact on individual patients	The impact on individual patient depends on the type of antibodies formed and the risk factors mentioned above. The potential lack of drug effect might result in prolonged neutropenia or incidence of febrile neutropenia, which might have serious clinical consequences such as life-threatening infections.
Potential Public health impact of safety concern	None.
Evidence source and strength of evidence	All therapeutic proteins have potential for immunogenicity. Binding antibodies do occur with efbemalenograstim alfa as expected with all biologics; however, they have not been associated with neutralising activity at present and no effect on the pharmacokinetics has been observed in clinical trials. The detection of ADA is technically challenging, and all assays have limitations, namely a limited capacity in detecting ADA in the presence of a drug due to IC formation, which may underestimate the ADA incidence. [14] The immunogenic potential of a biological medicinal product is difficult to predict, as the manufacturing process itself may influence the immunogenicity, depending on the cell line, growth media and conditions, as well as the post-translational modification of the biomolecule. [19] The current knowledge about immunogenicity of biological products supports the possibility of causal relationship of this risk with efbemalenograstim alfa, however, clinical trials did not reveal an impact of ADA on drug effect or occurrence of

	adverse reactions. Considering a large variety of factors that might affect ADA formation, its detection and clinical presentation, it is expected that the data from real-life population will provide more scientific evidence to further characterise/confirm this risk.
Impact on the benefit/risk balance of the product	The current impact on benefit/risk balance is acceptable.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Immunogenicity
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Routine pharmacovigilance activities will allow the monitoring and follow-up of any concern which may arise and facilitate the modification and/or planning of further actions than those detailed below. In any case, any eventual future recommendations from the PRAC, CHMP or Heads of Medicines Agencies (HMA) as well as National Competent Authorities (NCAs) on the proposed activities will be considered and applied. Consequently, the Pharmacovigilance Plan of the aforementioned product will be updated accordingly.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are sufficient to address any safety concerns, with the supplementary areas of focus described below:

As this product is a biological product, particular attention will be paid to the identification of product names and batch numbers during the collection and processing of Individual Case Safety Reports (ICSRs) in the post-marketing setting. This includes:

- Ensuring that training provided to Evive staff on collection of safety data includes a requirement to request confirmation of the product name and batch number;
- Ensuring vendors involved in pharmacovigilance activities are instructed to collect product names and batch numbers from ICSR reporters, e.g., medical information vendors, pharmacovigilance vendors;
- Ensuring that distribution and/or licensing partners involved in product commercialisation are instructed to collect product names and batch numbers from ICSR reporters.

These requirements will be documented in applicable company procedures and inter-company contractual documents, such as Pharmacovigilance Agreements and Safety Data Exchange Agreements. The nature of ICSR reporting in the post-marketing setting is such that reporters often do not provide this information. Evive is establishing options that would facilitate easy recording of product name and batch information for individual patient doses, hopefully increasing the likelihood of this information being available upon Evive' request. As part of the sub-section Traceability of Section 4.4 – Special warnings and precautions of the SmPC, instructions are provided to healthcare professionals to record the name of the administered product in the patient file in order to improve the traceability of the medicinal product. In line with the traceability and anti-counterfeiting requirements outlined in Commission delegated regulation (EU) 2016/161, a single 2D barcode will appear on the carton.

Evive will establish a signal detection process to review ICSRs collected in the post-marketing setting to detect any new safety concerns or any changes in understanding of existing safety concerns. This methodology will be supplemented by a review of data stratified by reported batch numbers to determine if the safety profile demonstrates a significant difference between batches.

III.2 Additional pharmacovigilance activities

There are no planned additional pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

There are no planned additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Important potential risks

Safety concern	Routine risk minimisation activities
Immunogenicity	Routine risk communication: • SmPC Sec. 4.4 • PL Sec. 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Pack size: pack size of one pre-filled syringe with safety guard • Prescription only medicine

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of risk minimisation measures

Not applicable.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern		Risk minimisation measures	Pharmacovigilance activities
Important potential risks	Immunogenicity	Routine risk minimisation measures: *SmPC section 4.4* *PL Section 2, Warnings and precautions*	Routine pharmacovigilance activities

Part VI: Summary of risk management plan for Ryzneuta® (Efbemalenograstim alfa)

This is a summary of the risk management plan (RMP) for Ryzneuta. The RMP details important risks of Ryzneuta, how these risks can be minimised, and how more information will be obtained about Ryzneuta's risks and uncertainties (missing information).
Ryzneuta's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Ryzneuta should be used.
This summary of the RMP for Ryzneuta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Ryzneuta's RMP.

I. The medicine and what it is used for

Ryzneuta is authorised in the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes). It contains efbemalenograstim alfa as the active substance and it is given by subcutaneous injection via a pre-filled syringe for manual administration.

Further information about the evaluation of Ryzneuta's benefits can be found in Ryzneuta's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Ryzneuta, together with measures to minimise such risks and the proposed studies for learning more about Ryzneuta's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.
For Ryzneuta, no risks that would require activities beyond routine risk minimisation measures or routine pharmacovigilance activities were identified.

II.A List of important risks and missing information

Important risks of Ryzneuta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ryzneuta. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	None
Important potential risks	Immunogenicity
Missing information	None

II.B Summary of important risks

Important identified risks: None	
Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	All therapeutic proteins have potential for immunogenicity. Binding antibodies do occur with efbemalenograstim alfa as expected with all biologics; however, they have not been associated with neutralising activity at present and no effect on the pharmacokinetics has been observed in clinical trials. The detection of ADA is technically challenging, and all assays have limitations, namely a limited capacity in detecting ADA in the presence of a drug due to IC formation, which may underestimate the ADA incidence. [14] The immunogenic potential of a biological medicinal product is difficult to predict, as the manufacturing process itself may influence the immunogenicity, depending on the cell line, growth media and conditions, as well as the post-translational modification of the biomolecule. [19] The current knowledge about immunogenicity of biological products supports the possibility of causal relationship of this risk with efbemalenograstim alfa, however, clinical trials did not reveal an impact of ADA on drug effect or occurrence of adverse reactions. Considering a large variety of factors that might affect ADA formation, its detection and clinical presentation, it is expected that the data from real-life population will provide more scientific evidence to further characterise/confirm this risk.
Risk factors and risk groups	In general, the immunogenicity of therapeutic proteins can be influenced by many factors, including the genetic background of the patient, the type of disease, the type of protein, the presence of conjugates or fragments, the route of administration, dose frequency, and duration of treatment. [15]
Risk minimisation measures	*SmPC section 4.4* *PL Section 2*
Additional pharmacovigilance activities	Not applicable
Missing Information: None	

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Ryzneuta.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Ryzneuta.

Annex 4 - Specific adverse drug reaction follow-up forms

No specific adverse event forms are associated with this RMP

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable