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Short Communication

Efbemalenograstim alfa, a long-acting granulocyte colony-stimulating factor, a novel dimeric G-CSF Fc fusion protein for reducing the risk of febrile neutropenia following chemotherapy

Simon Xi-Ming Li[1], Qing-Song Hou[1], Shu-Fang Wang[1], Jian-Min Chen[1], Wei Yao[1], Yan-Yan Fu[1], Li- Chuan Liu[1], Ren-Shu Li[1], Han Yang Chen[2], Kai Yang Tang[2], Xiao Qiang Yan[2,*]

[1]Evive Biotechnology (Shanghai) Ltd. Building 2-B, 797 Puxing Hwy, Minhang, Shanghai, China

[2]ITabMed (Shanghai) Ltd. Bld C9, 2555 Xiupu Road, Pudong, Shanghai, China

*Author for correspondence: Email: xiaoqiang.yan@itabmed.com

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Abstract

The long-acting rhG-CSFs i.e. pegfilgrastim can reduce the frequent injection burden of the short-acting filgrastim with similar clinical benefits. However, there remains a challenging gap of unmet need in effective management of chemotherapy-induced neutropenia (CIN). Ryzneuta™ (Efbenmalenograstim alfa, F-627), a novel long-acting dimeric rhG-CSF Fc fusion protein without pegylation, was recently approved in China, showing several advantages over currently approved rhG-CSF products.

Demonstrated by 12 clinical studies conducted globally, Ryzneuta™ can provide cancer patients with a more effective, safe, accessible, affordable, and convenient alternative treatment especially in managing CIN.

Keywords: Efbenmalenograstim alfa, RyzneutaTM, F-627, G-CSF, neutropenia, CIN

Short Communication

Chemotherapy-induced neutropenia (CIN) can cause life-threatening complications such as febrile neutropenia (FN) or other infections. Patients who develop FN often require prolonged hospitalizations and treatment with broad-spectrum antibiotics. Guidelines recommend that risk for FN should be assessed for patients based on disease setting and chemotherapy regimen prior to treatment. Patients with high-risk for FN (>20%) should receive prophylactic granulocyte colony-stimulating factor (G-CSF) products [1,2].

Several subcutaneously administered human granulocyte colony-stimulating factor (G-CSF) drugs have been marketed to manage neutropenia including the short- and long-acting recombinant human G-CSF (rhG-CSF) and biosimilars. The short-acting rhG-CSFs including filgrastim [3] and its biosimilar products are administered to patients daily after chemotherapy and are widely used in the developing countries to manage CIN. The long-acting rhG-CSFs including pegfilgrastim [4], lipegfilgrastim [5] and eflapegrastim [6] are administered only once per chemotherapy cycle because the half-life was extended to 30-50 hours through protein pegylation technology. Although pegfilgrastim and its biosimilars can show similar clinical benefits and reduce the frequent injection burden compared with the short-acting filgrastim, effective management of CIN in patients in clinical settings remains challenging. A drug candidate with a novel mechanism of action would have a great potential to further improve the clinical outcome for patients, highlighting a significant unmet need.

Efbemalenograstim alfa (Ryzneuta™, F-627), is a dimeric rhG-CSF Fc fusion protein developed to more effectively manage CIN in cancer patients. Ryzneuta™ was first approved last week by the

Chinese regulatory agency, NPMA to treat CIN and has several advantages compared to currently available biologics. The unique dimeric rhG-CSF structure of Ryzneuta™ is thought to generate a stronger biological response at the G-CSF receptor, ultimately acting as a more potent stimulant of neutrophil production and reducing the incidence of CIN in patients. In addition, due to its fusion to an Fc-chain, Ryzneuta™ is long-acting, enabling once per chemotherapy cycle dosing.

A total of 12 clinical studies have been completed with Ryzneuta™. These studies include four Phase I studies in healthy volunteers and eight studies (3 Phase I, 2 Phase II, and 3 Phase III) in cancer patients. The studies were conducted in 7 countries including China, USA, Ukraine, Russia, Hungary, Bulgaria, and Australia. Across these clinical studies, a total of 727 breast cancer patients have been treated with SC administered F-627. Ryzneuta™ was administered once per chemotherapy cycle. In Chinese studies, F-627 clinical trials were conducted head-to-head with short-acting filgrastim and the primary and secondary endpoints were met. In the global (outside China) studies, F-627 was tested head-to-head with long-acting pegfilgrastim and the primary and secondary endpoints were also met. The detailed clinical studies will be published elsewhere.

In the F-627 China registration study, a multicenter, randomized, open-label, active-controlled, non-inferiority phase III study conducted was designed to evaluate the efficacy and safety of a single subcutaneous injection of F-627 20 mg versus daily subcutaneous injection of filgrastim (GRAN®) 5 μg/kg/day in prophylactic treatment of chemotherapy-induced neutropenia in Chinese patients with breast cancer receiving up to four cycles of chemotherapy with epirubicin and cyclophosphamide (NCT04174599). The primary endpoint was the duration of grade 3 or 4 neutropenia in cycle 1, which occurred at 0.68 (1.10) and 0.71 (0.97) days for the F-627 and the filgrastim groups, respectively. Results for all efficacy endpoints in cycles 2–4 were generally consistent with the results in cycle 1. A trend towards a lower incidence and a shorter duration of grade 3 or 4 neutropenia and grade 4 neutropenia was observed in F-627 compared with filgrastim. A single fixed dose of 20 mg of F-627 in each cycle was as safe and effective as a daily dose of filgrastim in reducing neutropenia and its complications.

In the F-627 global registration studies, 2 global phase III studies were conducted outside China. GC- 627-04 study was a multicenter, randomized, double-blind, placebo-controlled study (NCT02872103). The results show that F-627 is effective and safe in breast cancer patients receiving TA chemotherapy. Superiority of F-627 over placebo was seen for the primary endpoint of mean duration of severe neutropenia (DSN) in cycle 1, with patients experiencing 1.3 days and 3.9 days in F-627 and placebo treated groups, respectively (95% CI:2.3,3.4). These data were supported by additional secondary endpoint outcomes, such as incidence of FN, SN, and ANC nadir in cycle 1. The incidence of FN in cycle 1 was much lower in F-627 group (4.8%) than in placebo group (25.6%) ($p = 0.0016$; tested at $\alpha = 0.04$). The incidence of SN in cycle 1 was 69.9% and 94.9% in F-627 group and placebo group respectively ($p = 0.0019$; tested at $\alpha = 0.001$). In cycle 1, the mean depth of ANC nadir was 0.7×10^9/L and 0.2×10^9/L, respectively (95%CI: 2.0, 5.6).

GC-627-05 was a global phase III, two-arm, open-label clinical study being conducted in females with Stage I-III breast cancer who were receiving neo-adjuvant or adjuvant myelotoxic TC chemotherapy treatment (docetaxel + cyclophosphamide, 75 and 600 mg/m^2, respectively) (NCT03252431). The primary endpoint was the mean duration of Grade 4 (severe) neutropenia in chemotherapy cycle 1. F-627 at 20 mg fixed dose once per chemotherapy cycle was shown to be statistically non-inferior to pegfilgrastim (Neulasta®) in reducing the duration of severe neutropenia in Cycle 1. The results showed that the mean duration of severe neutropenia was 0.2 days for both F-627 and Neulasta®. The mean difference (SD) in the duration of Grade 4 (severe) neutropenia in chemotherapy cycle 1 between F-627 and Neulasta®, assessed using multiple imputation, was 0.0 (0.05) days (95% CI: -0.1, 0.1), with $p = 0.7074$. Further analysis of main secondary efficacy and safety variables demonstrated that F-627 was comparable to Neulasta® in other protocol-defined secondary endpoints and safety with additional clinical benefits.

In three pivotal phase III studies, patients randomized to the F-627 group received a single subcutaneous injection of F-627 20 mg per chemotherapy cycle on day 2 or 3 of each cycle, approximately 24 or 48 hours after receiving one standard dose of chemotherapy. This flexible administration window could reduce patients' hospitalization days and lower the medical expenses, as current approved G-CSF drugs in China are restricted to administration 48 hours after chemotherapy. Recent preclinical studies indicate that F-627 may be suitable for same-day dosing after the completion of chemotherapy, which could significantly enhance patient compliance and reduce medical costs.

Although the two phase III registration studies of F-627 were conducted with a non-inferiority study design to compare with filgrastim (China study) and pegfilgrastim (global study) as the primary endpoints, a significant clinical benefits were observed in the F-627 study arm such as lower incidence and shorter duration of grade 3 or 4 neutropenia, higher ANC nadir and less chemo dose reduction suggesting the biological contribution of dimeric rhG-CSF design with enhanced activity in patients.

In summary, F-627 is a novel long-lasting dimeric rhG-CSF-Fc protein developed to stimulate neutrophil production and prevent complications of CIN in cancer patients. The novel design of F-627 provides cancer patients with a number of novel clinical benefits that are not possible with current G-CSF acting drugs, such as flexible, once-per cycle dosing. In addition, F-627 is manufactured in CHO cell lines and its unique dimeric fusion protein structure does not require pegylation, mitigating potential risks that come with PEG protein modification. Additionally, the manufacturing of F-627 has much simpler process compared to that pegylated G-CSF molecules, therefore enabling increased accessibility and affordability to long half-life G-CSF treatment to more patients worldwide. Finally, F-627 has demonstrated robust safety profile. A wealth of robust F-627 data across the studies contributes to have it expected to be a promising more effective and convenient alternative long-acting G-CSF for oncologists to support cancer patients receiving chemotherapy, especially in China and other developing countries where Neulasta® is not available to patients.

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