GaBiJournal
Generics and Biosimilars Initiative Journal

Pelmeg®, a biosimilar pegfilgrastim developed in the context of evolving regulatory guidelines

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Pelmeg® is a biosimilar pegfilgrastim, which obtained European Union (EU) regulatory approval in September 2018, with marketing beginning in January 2019. A comprehensive analytical, functional and preclinical comparability programme demonstrated a high degree of similarity between Pelmeg® and its reference product Neulasta®. A targeted clinical development programme was conducted with Pelmeg®, consisting of two comparative pharmacokinetic (PK)/pharmacodynamic (PD) studies in healthy subjects. Since a surrogate endpoint for efficacy (absolute neutrophil count [ANC]) was available, efficacy and safety studies in patients were waived by the regulatory authorities. Clinical studies with Pelmeg® were designed in close dialogue with regulatory authorities in Europe. During the development process for Pelmeg®, the EU biosimilar guidelines, in particular relating to granulocyte colony-stimulating factor (G-CSF), were modified. The development of Pelmeg® demonstrates that regular discussions with regulators, in the form of scientific advice or other interactions, are valuable opportunities for dialogue regarding scientific progress related to the comparability of biosimilars. Regulators – at least in the area of biosimilar development – were found to be open to improvements and to deviate from existing guidelines if there was agreement that the scientific state-of-the-art has superseded some aspect of the guidelines. Overall, we suggest that abridged development programmes waiving the need for phase III studies, as described for Pelmeg®, are possible, in particular if good surrogate endpoints are available. In line with this, the number of waivers for phase III studies in biosimilar development has increased in recent years.

Keywords: Biosimilar, filgrastim, Neulasta®, pegfilgrastim, Pelmeg®, targeted development

Introduction

A biosimilar can be defined as a biological medicine that is similar to an already authorized biological medicine (the reference medicinal product). A science-based regulatory framework to ensure development of high quality biosimilars was established in Europe in 2005; and is monitored and updated on an ongoing basis [1, 2]. In line with the aforementioned guidelines, similarity to the reference medicinal product must be established in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise.

The development of a biosimilar is a multi-step process that is tailored to the individual product. Similarity to the reference medicinal product is demonstrated using a totality-of-evidence approach in a stepwise manner across the three major pillars of development: quality, non-clinical and clinical. First, analytical similarity between test and reference product must be demonstrated on the physicochemical and biofunctional levels via a comprehensive similarity exercise. Next, similarity is investigated by comparative non-clinical studies. Finally, once the similarity of test and reference product has been established on the quality and non-clinical levels, comparable clinical performance must be confirmed.

The overall aim of the comparability exercise is not to demonstrate the 'efficacy and safety' of the biosimilar, but to confirm the absence of clinically meaningful differences (for example, in immunogenicity) to the reference product. The extent and nature of the clinical studies is highly dependent on the level of evidence obtained in the previous step(s), including the robustness of the physicochemical, biological and non-clinical *in vitro* data [3]. Overall, the comparability exercise should be individually tailored to the molecule. Factors affecting the number and types of clinical studies required for regulatory approval include the complexity of the molecule and comparability of the available data, as well as the availability of a pharmacodynamic (PD) endpoint which correlates with efficacy [4].

Development approach for the pegfilgrastim biosimilar Pelmeg®

Pelmeg® (development code B12019) is a biosimilar pegfilgrastim to EU-authorized Neulasta®. Pelmeg® obtained regulatory approval in the European Union (EU) in 2018 for the same indications as the originator, Neulasta®: 'Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (except for chronic myeloid leukaemia and myelodysplastic syndromes)'.

Pegfilgrastim is a long-acting, pegylated form of human recombinant granulocyte colony-stimulating factor (G-CSF; filgrastim), which is expressed by *Escherichia coli (E. coli)*. Filgrastim, the protein moiety of pegfilgrastim, has an identical amino acid sequence to endogenous human G-CSF, except for an additional N-terminal methionine residue which is required for expression in *E. coli* (r-metHuG-CSF). Pelmeg® is delivered in the same formulation as Neulasta® (pre-filled syringes containing 6 mg of the active substance in 0.6 mL solution for injection) and administered as a subcutaneous (SC) injection.

This manuscript describes the targeted approach used for development of Pelmeg®, which led to its approval in the EU in 2018. Of note, since a surrogate endpoint for efficacy was available, the clinical development programme of Pelmeg® was limited to pharmacokinetic (PK) and pharmacodynamic (PD) studies, while phase III studies were waived.

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Submitted: 13 May 2020; Revised: 6 July 2020; Accepted: 7 July 2020; Published online first: 20 July 2020

Summary of analytical characterization

After full characterization of the reference product Neulasta®, the biosimilarity of Pelmeg® to Neulasta® was assessed by a head-to-head analytical characterization. State-of-the-art, orthogonal analytical methods were employed to characterize the structural and functional characteristics of both drugs and to demonstrate analytical similarity between Pelmeg® and the reference product. The stability and degradation profiles of the molecules were also compared.

The potency of Pelmeg® and Neulasta® was analysed using a cell proliferation assay, which measured the biological activity of the pegfilgrastim based on its binding to, and induction of the proliferation of, specified cells. This assay determines the potency of human modified G-CSF, i.e. pegylated G-CSF, using a specified cell line, which proliferates only in the presence of G-CSF. The method was closely aligned with the European Pharmacopoeia potency assay for filgrastim [5]. The functional similarity of Pelmeg® and Neulasta® was assessed by binding to the recombinant human G-CSF receptor (rhG-CSFR) using surface plasmon resonance (SPR). Results from the analytical characterization are summarized in Table 1.

Table 1: Summary of similarity results for physicochemical and biofunctional testing of Pelmeg® versus Neulasta®

Quality attribute	Parameter	Analytical method for control and characterization	Conclusion
Primary structure	Primary sequence	LC-MS and Edman	Identical
	Disulphide bonding pattern comparison	LC-MS	Similar
Intact mass and pegylation	Pelmeg® intact mass	LC-MS	Similar
	Molecular weight	Capillary SDS-PAGE (CGE)	Similar
	Positional pegylation	LC-MS/Edman	Identical
	PEG polydispersity	ESI-MS	Similar
	PEG identity comparison	SDS-PAGE titrisol	Similar
Higher order structure	Secondary and tertiary structure comparison	Circular dichroism	Similar
	Tertiary structure comparison	Differential scanning calorimetry	Similar
		Intrinsic fluorescence spectrometry	Similar
Purity and impurities – product related variants	Charge variants	CEX-HPLC	Similar
		Isoelectric focussing	Similar
	Purity and impurities	RP-HPLC	Similar
	Methionine oxidation	UPLC-UV-MS	Slight differences observed for Pelmeg®, but not considered clinically meaningful nor critical for scientific evaluation of similarity
	Low molecular weight (LMW) and high molecular weight (HMW) species	Western blot	Similar
		SEC-HPLC	Similar
		Analytical ultracentrifugation	Similar
Purity and impurities – other impurities	Residual free PEG	RP-HPLC-ELSD	Similar
General properties	Extinction coefficient	RP-HPLC followed by fluorescence	Similar
	Protein content comparison	UV/VIS	Similar
	Osmolality comparison	Ph. Eur. 2.2.35	Similar
	Extractable volume	Ph. Eur. 2.9.17	Similar
Biofunctional testing	Potency	Cell-proliferation assay	Similar
	Receptor binding	Surface plasmon resonance	Similar

CEX: cation exchange; CGE: capillary gel electrophoresis; ELSD: evaporative light scattering detection; ESI: electrospray ionization; HPLC: high performance liquid chromatography; LC: liquid chromatography; MS: mass spectrometry; PEG: polyethylene glycol; Ph. Eur.: Pharmacopoea Europaea; RP: reversed phase; SDS-PAGE: sodium dodecyl sulfate polyacrylamide gel electrophoresis; SEC: size-exclusion chromatography; UPLC: ultra performance liquid chromatography; UV: ultraviolet; VIS: visible.
Source: European Public Assessment Report, Pelmeg® [6].

The primary structure of Pelmeg® was confirmed to be identical to that of Neulasta®, with an identical pegylation site. Molecular weight and polydispersity indicated similar polyethylene glycol (PEG) moieties between Pelmeg® and Neulasta®. The higher order structure, product-related variants, and the impurity and aggregation profiles were also shown to be similar. Furthermore, relative potency and recombinant human G-CSF receptor binding kinetics were similar for Pelmeg® and Neulasta®. Comparative stability testing demonstrated that Pelmeg® and Neulasta® degrade in a comparable manner. Overall, the results of the physicochemical, biofunctional and stability tests met regulatory criteria for assuming the similarity of Pelmeg® to Neulasta®.

Of note, the quality comparability data were assessed in depth by the European Medicines Agency (EMA) during the review of the marketing authorisation application (MAA) dossier for Pelmeg®. The European Public Assessment Report for Pelmeg® [6] states: 'In general, all quality attributes analysed proved to be highly similar between Pelmeg and EU Neulasta. For a few parameters slight differences were observed. However, these differences were properly justified and shown to have no impact on safety or efficacy of the product. Importantly, functional testing showed high similarity between both products. From a quality point of view Pelmeg® can be considered as biosimilar to EU Neulasta'. Subsequent non-clinical and clinical studies were performed to address any residual uncertainty regarding biosimilarity. The extent and nature of these studies was determined by the results from analytical similarity testing.

Summary of non-clinical studies

Based on the high level of similarity on the physicochemical level, the non-clinical study programme focused on *in vitro* pharmacology studies (comparative biopotency and receptor binding studies, as described above) as well as one comparative PK/PD study in rats.

Toxicity studies in animals were not performed as the sponsor did not consider such studies to be sufficiently sensitive for detection of differences between Pelmeg® and Neulasta®, given their high level of similarity on the physicochemical and biofunctional levels. This was in line with EMA guidance in place at that time. Carcinogenicity, genotoxicity and reproductive toxicity studies were not required, as per EMA guidance for biosimilar development, and were not performed for Pelmeg® [7].

A good laboratory practice (GLP)-compliant, comparative single-dose PK/PD study of Pelmeg® in healthy and neutropenic rats was conducted in 2015 (this study was initiated prior to the scientific advice meetings held to discuss Pelmeg®'s clinical development). This study was designed to complement *in vitro* biofunctional data with *in vivo* data on PD-related parameters and to generate data on dose-dependent effects. Results from this study demonstrated that Pelmeg® and Neulasta® exhibited a high degree of similarity, based on a comparison of PK (area under the concentration time curve [AUC], maximum concentration [C_{max}]) and PD (area under the effect time curve [AUEC], maximum effect [E_{max}]) parameters.

Summary of clinical studies

While the clinical studies with Pelmeg® were being designed and conducted (2015–2017), various guidelines provided recommendations for the clinical development of (peg)filgrastim. These are introduced below, followed by a description of the Pelmeg® clinical programme.

Regulatory framework for clinical studies

1. Guideline on similar biological medicinal products 2014, EMA [1].
This guideline advises that *'studies should be sensitive enough with regard to design, conduct, endpoints and/or population to detect such differences. In specific circumstances, a confirmatory clinical trial may not be necessary. This requires that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern'.* The guideline also recommends discussing tailored approaches to development with regulatory authorities.

2. Original biosimilar guideline 2006, EMA [8]: This guideline mandates efficacy and safety trials in patients.
'Efficacy trials
Usually comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biological and the reference medicinal product. Clinical comparability margins should be prespecified and justified, primarily on clinical grounds'.
'Clinical safety and PV requirements
Even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a difference in the safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Prelicensing safety data should be obtained in a number of patients sufficient to address the adverse effect profiles of the test and the reference medicinal product'.

3. In 2013, a draft revision of this guideline [7] was published.
This revised guideline stated that efficacy and safety should be shown in clinical trials in patients: *'Usually, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference medicinal product in adequately powered, randomised, parallel group comparative clinical trial(s), preferably double-blind.* […] *Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety profile. Clinical safety is important throughout the clinical development programme and is captured during initial PK and/or PD evaluations and also as part of the pivotal clinical efficacy study establishing comparability. Comparative safety data should normally be collected pre-authorisation, their amount depending on the type and severity of safety issues related to the reference product'.*
In December 2014, a final revision of the guideline was published, see below [2].

4. Biosimilar guideline from 2014, EMA [2]:
This guideline states that *'The clinical biosimilar comparability exercise is normally a stepwise procedure that should begin with pharmacokinetic (PK) and, if feasible, pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, confirmatory PK/PD studies for demonstrating clinical biosimilar comparability'.*

The guideline states that confirmatory PK/PD studies may be sufficient if an accepted surrogate marker for efficacy is available. It explicitly mentions absolute neutrophil count (ANC) as a validated and accepted biomarker for the efficacy of G-CSF.

5. A G-CSF product specific annex (2006) to the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues, EMA [9].
This annex provides guidance on the choice of PK and PD parameters to be investigated in PK/PD studies with (peg)filgrastim. Moreover, the document recommends clinical trials in patients to show comparability in efficacy and safety. For efficacy, the recommended clinical model for the demonstration of comparability of the test and the reference medicinal product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (in terms of tumour type, previous and planned chemotherapy, as well as disease stage). For safety reasons, it is recommended to collect safety data from a cohort of patients after repeated dosing preferably in a comparative clinical trial.

6. A concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant G-CSF, EMA, 2015 [10].
This concept paper recommended revisions to the guidance on similar medicinal products containing recombinant G-CSF. Prerequisites for waiving a confirmatory clinical trial, including clinical safety/immunogenicity, are discussed.

In summary, at the time the Pelmeg® clinical studies were being designed, it was not clear from the guidelines that clinical trials in patients could be waived altogether, although some prerequisites for waiving such a trial, e.g. PD marker ANC, are mentioned in the guidelines.

Clinical studies with Pelmeg®

The clinical development programme for Pelmeg® was designed and conducted using a sensitive comparability approach, waiving clinical efficacy studies in patients. This approach was chosen because an accepted surrogate marker is available for G-CSF (ANC), which was used as a surrogate for efficacy in the clinical development of Pelmeg®. This clinical approach is furthermore supported by the prerequisite demonstrations of similarity on the physicochemical, biofunctional, and preclinical PK/PD levels. Two clinical studies were conducted in the development of Pelmeg®, see Table 2.

The pivotal study (B12019-101) was a single-dose, randomized, double-blind, two-stage, two-way crossover PK and PD study at a dose of 6 mg. This study enrolled 172 healthy subjects and assessed PK and PD as co-primary endpoints. A comprehensive immunogenicity assay programme, based on the latest science on immunogenicity testing, was also implemented in the study.

The supportive study (B12019-102) was a multiple-dose, randomized, double-blind, three-period, two-sequence crossover study to assess the immunogenicity and PD comparability of Pelmeg® and Neulasta® at a dose of 3 mg. This study enrolled 96 healthy subjects and assessed PD and immunogenicity as co-primary endpoints. It included a multiple-dose parallel-group study in order to detect differences in immunogenicity, using a sensitive set of assays for immunogenicity testing.

All studies were conducted in line with good clinical practice (GCP) guidelines and EU regulatory standards. Of note, the clinical programme was designed considering scientific advice obtained from several national regulatory authorities in the EU, and in particular EMA. These scientific advice meetings were held between January and June 2015. Only the two PK/PD clinical studies were required by EMA.

Crucial design aspects of the clinical studies

The mechanism of action of pegfilgrastim is the same in the target population (cancer patients undergoing chemotherapy) and healthy subjects, whereby pegfilgrastim elicits its effects on haematopoietic cells by binding to specific cell surface receptors, stimulating proliferation and differentiation of committed progenitor cells of the granulocyte-neutrophil lineage into functionally mature neutrophils [11].

Table 2: Clinical studies with Pelmeg®

Study	Design	Study population	Dose and Regimen	Objectives/Endpoints
B12019-101 PK/PD study (pivotal)	Single-dose, randomized, double-blind, two-stage, two-way crossover study	172 healthy subjects	Single-dose SC Pelmeg® and Neulasta® (6 mg) Sequence 1: Pelmeg®-Neulasta® Sequence 2: Neulasta®-Pelmeg®	Co-primary: PK comparability based on $AUC_{0\text{-last}}$ and C_{max} PD comparability based on $AUEC_{0\text{-last}}$ for ANC Secondary: Additional PK and PD endpoints, immunogenicity, safety
B12019-102 PD and immunogenicity/ safety study (supportive)	Multiple-dose, randomized, double-blind, three periods, two sequences, cross-over study	96 healthy subjects	Multiple-dose SC Pelmeg® and Neulasta® (3 mg) Sequence 1: Pelmeg®-Pelmeg®-Neulasta® Sequence 2: Neulasta®-Neulasta®-Pelmeg®	Co-primary: PD comparability based on $AUEC_{0\text{-last}}$ for ANC, and immunogenicity/safety Secondary: PK, additional PD and immunogenicity endpoints

ANC: absolute neutrophil count; AUC: area under the concentration time curve; AUEC: area under the effect time curve; C_{max}: maximum concentration; PD: pharmacodynamics; PK: pharmacokinetic; SC: subcutaneous.

Both clinical studies were conducted in healthy subjects rather than in the target population. Compared to cancer patients receiving chemotherapy, healthy subjects do not have co-morbidities or co-medications and are not immunosuppressed. Healthy subjects therefore represent a more sensitive study population for assessments of immunogenicity, as well as for PK and PD comparisons. The use of a sensitive population is recommended by the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues [2]. As explained previously, the PD parameter ANC is a clinically accepted and validated surrogate marker for the assessment of efficacy [2], making an efficacy study with Pelmeg® unnecessary.

The 6 mg dose of pegfilgrastim used in the pivotal study is in the ascending part of the dose-response profile for AUC and C_{max} [12, 13], and is thus considered sufficiently sensitive for assessment of PK. To account for variability in the relevant PK parameters [13], the methodology of the pivotal study was based on a two-stage design, planning for a sample size re-calculation after completion of stage 1 and potential sample size adjustment for stage 2 [14, 15]. In stage 1 of the trial, 172 subjects were enrolled. After completion of the trial, PK was assessed, and an interim evaluation was performed. In the case of inconclusive results, additional subjects would have been enrolled after a sample size determination based on data derived from stage 1. However, the interim evaluation revealed that stage 2 was not required.

In the supportive study, PD comparability was investigated at a dose lower than 6 mg (3 mg). This was based on the fact that a 6 mg dose alone may not be sufficiently discriminative for comparative investigations of PD between Pelmeg® and Neulasta®. The 3 mg dose selected is in the ascending part of the dose-response curve for PD [12, 16]. This is in line with scientific advice obtained from EMA, which suggested a dose in the range of 2–4 mg for the PD evaluation, 3 mg was chosen for operational reasons.

The supportive study applied a parallel-group crossover design in order to assess potential immunogenicity after repeat dosing. Subjects were dosed twice with Pelmeg® or Neulasta® (followed by a crossover to the other treatment), as the likelihood of the formation of anti-drug antibodies (ADAs) is higher after multiple dosing compared to a single dose.

General principles for the demonstration of bioequivalence were applied. The equivalence margin used in standard clinical bioequivalence studies (80.00%–125.00%) was considered appropriate for the PK and the PD parameters [17]. For the PD parameter, 95% confidence intervals (CIs) were used.

Overall, the results from the pivotal study demonstrated the comparability of Pelmeg® and Neulasta® for the primary PK and PD parameters, and results from the supportive study confirmed comparability of Pelmeg® and Neulasta® with regards to PD. The immunogenic potential of Pelmeg® and Neulasta® was comparable, and low in both. No antibodies directed against the filgrastim moiety of the molecule nor neutralizing antibodies were detected in either study. There was no observable impact of subjects' ADA status on PK parameters or PD response. The safety profile of Pelmeg® and Neulasta® was similar and in line with the published safety profile for Neulasta®.

Results from the two studies have since been published [18, 19]. Key PK and PD results from the two studies are summarized in Table 3 (Study B12019-101) and Table 4 (Study B12019-102).

A summary of the timeframe of the Pelmeg® clinical development programme is provided below (and in Figure 1), including interactions with regulatory authorities, evolvement of guidelines, and submission of the Pelmeg® MAA dossier and positive Committee for Medicinal Products for Human Use (CHMP) opinion.

- 2014: Existing regulatory guidelines (see Section 'Regulatory framework for clinical studies') appeared to be in need of reform, considering the latest science on comparability of G-CSF biosimilars.
- 2015 (January–June): Scientific advisory meetings were held with national regulatory authorities and EMA to discuss Pelmeg®'s clinical development, in which an agreement to waive clinical studies in patients was achieved.
- 2015 (July): A concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant G-CSF was published by EMA. This concept paper recommended

Table 3: Statistical analysis of primary PK parameters (model-based PK set, n = 161), and primary PD parameter (model-based PD set, n = 161) in study B12019-101

Parameter	Pelmeg®/Neulasta®		
	Ratio (%)	94.32% CI	Intra-subject CV (%)*
PK parameters			
$AUC_{0\text{-last}}$	95.2	86.6;104.7	46.7
C_{max}	92.8	84.4;102.2	47.1
PD parameter			
$AUEC_{0\text{-last}}$ of ANC	100.20	98.7;101.8	7.0

The model-based PK/PD sets included only subjects with data from both study periods, and without any protocol deviations which would render the data incomparable between treatments. Accordingly, all subjects who discontinued prematurely and had reliable data for one study period only were excluded from the model-based PK and/or PD set. In addition, subjects who could not provide full profiles (for PK and/or PD), e.g. due to missing visits, were excluded from the respective set.
*Intra-individual CV (%) estimated from the residual mean squares.

ANC: absolute neutrophil count; $AUC_{0\text{-last}}$: area under the concentration time curve from time zero to last measurable concentration; $AUEC_{0\text{-last}}$: area under the effect time curve from time zero to last measurable concentration; CI: confidence interval; C_{max}: maximum concentration; CV: coefficient of variation; N: number of subjects; PD: pharmacodynamics; PK: pharmacokinetic.

Table 4: Statistical analysis of primary PD parameter AUEC0-last of ANC (model-based PD set, N = 82) in study B12019-102

Pelmeg®/Neulasta®		
Ratio (%)	**95% CI**	**Intra-subject CV (%)***
101.59	99.58;103.63	7.49

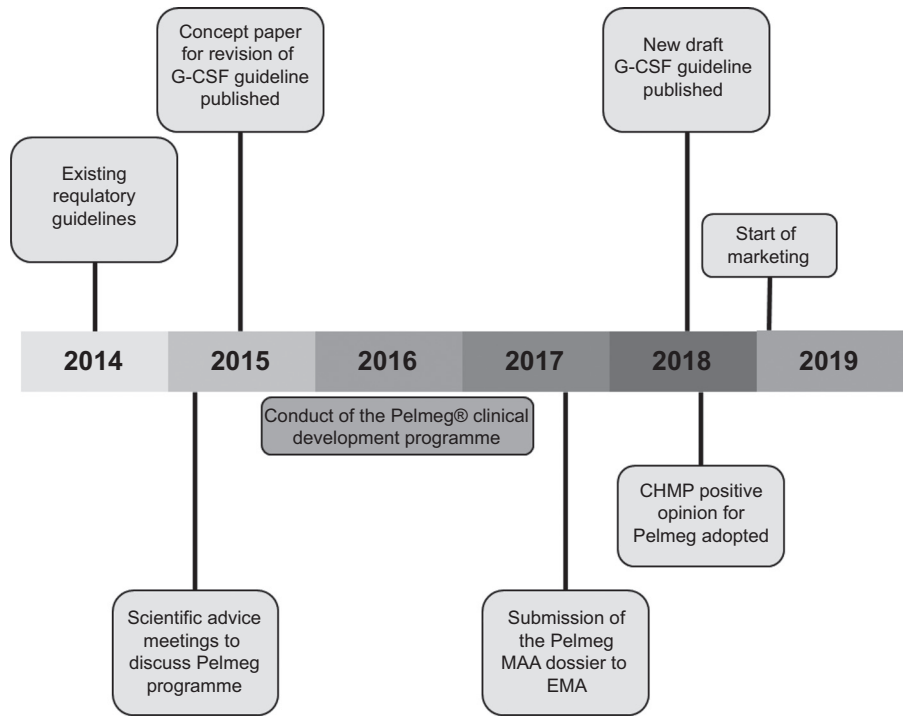
The model-based PD set included only subjects with reliable data from all three study periods.
*Intra-individual CV (%) estimated from the residual mean squares.

ANC: absolute neutrophil count; $AUEC_{0\text{-last}}$: area under the effect time curve from time zero to last available concentration; CI: confidence interval; CV: coefficient of variation; N: number of subjects; PD: pharmacodynamic.

revisions to the guidance on similar medicinal products containing recombinant G-CSF. Prerequisites for waiving a confirmatory clinical trial, including clinical safety/immunogenicity measures, were discussed.

- 2015 (August)–2017 (June): Conduct of the Pelmeg® clinical programme.
- 2017 (September): Submission of Pelmeg® MAA dossier.
- 2018 (August): A draft of the guideline for biosimilar development of G-CSFs was published by EMA, stating that efficacy and safety studies in patients are not necessary.
- 2018 (September): The CHMP adopted a positive opinion for Pelmeg®.
- 2019 (January): Marketing of Pelmeg® began.

Figure 1: Timeline of the Pelmeg® Clinical development program



CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; G-CSF: granulocyte colony-stimulating factors; MAA: marketing authorization application.

Overall, Pelmeg®'s clinical development was aligned with the revised EMA guidance on the development of pegfilgrastim biosimilars. Since Pelmeg® was launched, periodic reviews of its safety data have shown consistency with the originator. No new safety information has been identified.

Conclusion

The EMA guidelines have evolved with regard to the requirements for comparative clinical efficacy/safety studies in patients since their original implementation in 2005. In particular, the guideline for development of biosimilar G-CSFs now explicitly states that efficacy and safety studies in patients are not necessary. This revision relates to the fact that ANC can be used as a surrogate marker for efficacy. The availability of such a surrogate marker is rather unusual in biosimilar development and may enable reduced clinical development programmes.

As discussed, Pelmeg®'s development programme was guided by scientific discussion with regulatory authorities, including EMA. As demonstrated by the Pelmeg® development programme, scientific discussion with regulators – in the form of scientific advice or other interactions – are valuable opportunities for dialogue regarding scientific progress related to the comparability of biosimilars. Regulators – at least in the area of biosimilar development – were found to be open to improvements and to deviate from existing guidelines if there was agreement that the scientific state-of-the-art has superseded some aspect of these guidelines. However, it is always recommended to seek dialogue with regulatory bodies (especially in the form of scientific advice procedures) to discuss potential 'reforming steps' prior to implementing them in a clinical study protocol. Targeted/abridged development programmes, as described for Pelmeg®, are possible and based on sound scientific reasoning.

Over recent years, the number of waivers for phase III studies has increased [20-23]. Large and expensive phase III trials may be unable to detect clinical differences between biosimilars and originators. Indeed, there are examples where biosimilar products have failed PK/PD studies, while phase III studies have suggested similar efficacy between the biosimilar and originator [20, 24]. Reassuringly, despite regulatory changes to biosimilar drug development, after more than 10 years of experience in the EU, there have been no cases of withdrawal of an approved biosimilar, nor any changes to labelling due to efficacy or safety concerns [25].

Competing interests: The Pelmeg® studies were sponsored by Cinfa Biotech (now Mundipharma). The authors were employees of or consultants to Cinfa Biotech at that time. Medical writing activities were supported by Mundipharma Research Limited.

Provenance and peer review: Not commissioned; externally peer reviewed.

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DOI: 10.5639/gabij.2020.0903.021