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A REVIEW ON: NOVEL DRUG DELIVERY TECHNOLOGY OF PEGFILGRASTIM

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ABSTRACT

Pegfilgrastim is used to treat patients who are undergoing chemotherapy, in the case of neuropenia can reduce the incidence of infection. Pegfilgrastim is a longer acting form of filgrastim and the manufacturer recommends that it should not be administered within 14 days before chemotherapy. This review article focuses on drug delivery technology of Pegfilgrastim (production and formulation). Filgrastim in combination with PEG formula Filgrastim (being Pegfilgrastim) will further improve the stimulator of GCF.

KEYWORD: Pegfilgrastim, Filgrastim, Anti-cancer, Production, Formulation.

INTRODUCTION

Pegfilgrastim is used to treat patients who are undergoing chemotherapy, in the case of neuropenia can reduce the incidence of infection.[1] Neutropenia is a serious complication that often occurs in chemotherapy, especially in the elderly.[1] In addition to killing cancer cells, chemotherapy destroys normal cells.[2] A substantial decrease of neutrophils, a type of white blood cells, making the body unable to defend themselves against most types of infections.[2]

These drugs are used to stimulate the growth of white blood cells "healthy" in the bone marrow after chemotherapy is given.[1] White blood cells help the body to fight infection. This is not a chemotherapy drug.[1]

These drugs are usually given at least 24 hours after chemotherapy to stimulate the growth of new white blood cells (WBC) is healthy.[2]

Pegfilgrastim is a longer acting form of filgrastim and the manufacturer recommends that it should not be administered within 14 days before chemotherapy.[2] Pegfilgrastim administered as a single injection.[2] Pefilgastrim more profitable than the white blood cell stimulation products.[2] Approximately 1.4 million cancer patients in the United States in 2001, neutropenic infection protection is very important for parents, which in the next 20 years, will represent the majority of patients who receive chemotherapy.[2]

Production

These drugs can be given as an injection under the skin (subcutaneously), the syringes already filled. Pegfilgrastim dose depending on the severity of the cancer patients.[2]

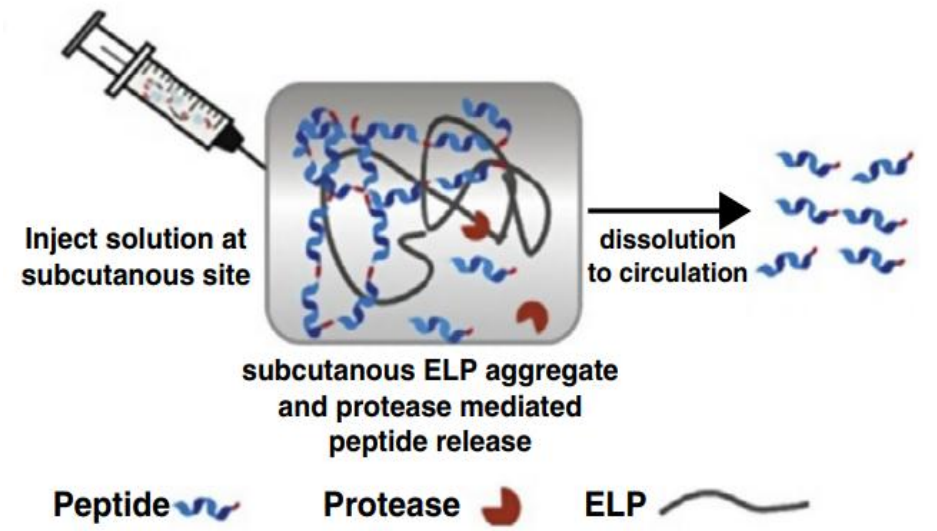

Figure 1: Subcutaneous injection of the Pegfrastim.[4]

Formulation

PEGylation early studies established PEG as a ‘stealth’ polymer, as defined by its ability to effectively prolong the in vivo circulation half-life and mask the immunogenicity of biomolecules.[4] In applications where the molecular weight (MW) of the conjugated PEG is chosen to be greater than renal clearance so as to confer a long circulation half-life of the drug.[4] Richter and Akerblom reported in 1983 that antibodies to PEG and ovalbumin were raised in rabbits immunized with PEGylated ovalbumin, though PEG alone of several different molecular weights (MWs) showed no or poor immunogenicity in rabbits and mice

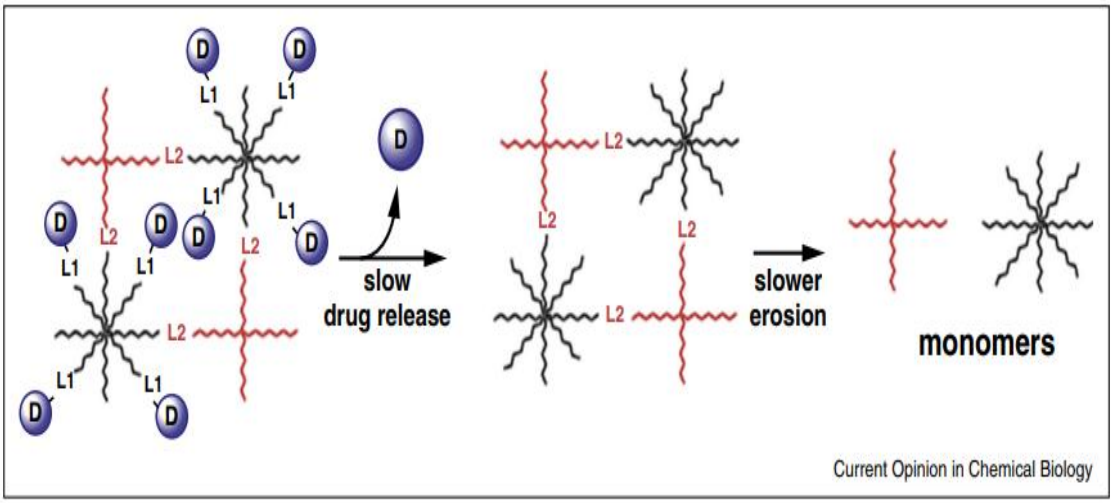

Figure 2: Hydrogels formed by tethering drugs to and cross-linking multi-arms of PEG macromonomers with cleavable b-eliminative linkers. Varying chemistry of the linker enables tunable drug release and depot degradation.[4]

Polycarbonates have recently gained much interest for protein/peptide conjugation because of their biodegradability and synthetic ease[4] Side-chain functionalization can be done either pre-polymerization or post-polymerization, with the latter option offering more tolerance to different substituents.[4] The versatility of this highly modular approach was demonstrated by synthesis of a range of functional polycarbonates, which are of particular relevance to peptide/ protein–polymer conjugates, such as polycarbonates with PEG, hydroxyl-containing and zwitterionic side-chains, all of which demonstrated promising protein-resistant properties and toxicity profiles.[4]

Covalent bonding of proteins with poliethylene glycol (PEG) has been the strategy of drug that is widely used, with the hope of improving the pharmacological characteristics of the therapy.[5] Some of the drugs approved for clinical use PEGasparaginaseeg, PEG interfero. The beneficial effect of PEG-conjugated PEG is given by the unique nature itself. PEG-conjugated polymers tend comprehensive as chain flexibility and hydration.[2] PEG is considered suitable for derivitisasifilgrastim. The goal is to control the elimination through the kidneys. Other reasons PEG relatively inert and has proven to be acceptable toxicological profile.[2]

Recombinant protein technology to connect between pharmacokinetics and pharmacodynamics properties of molecules. Interest engineering proteins which have

improved therapeutic characteristics different from a simple used as a substitute for natural equivalent.[5] The addition of polyethylene glycol (PEG) to filgrastim (G-CSF rmetHu) produces pegfilgrastim development. Pegfilgrastim is a long-acting form of filgrastim.[2] PEG covalent bonding to the Nterminal amine groups of molecules used to be in the reduction alkylation. This prolongs the half-life median pegfilgrastim up to 42 hours.[1]

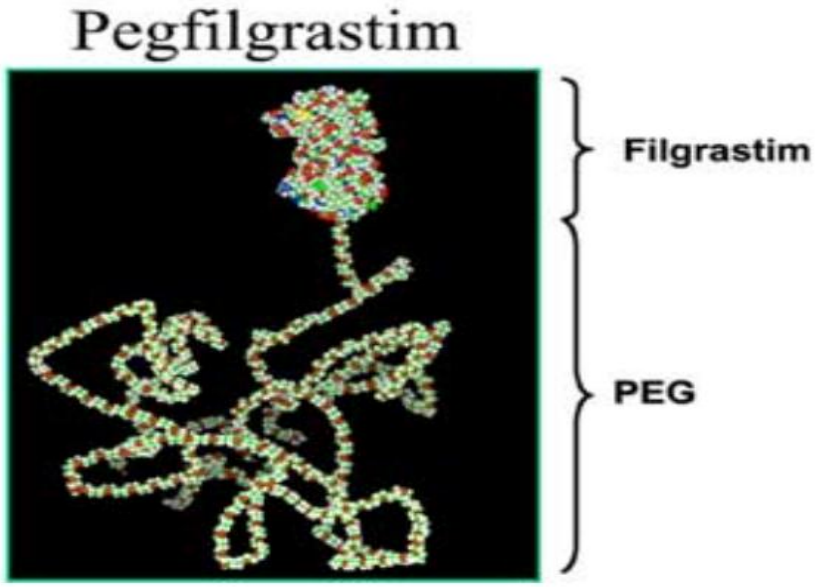

Figure 3: Model pegfilgrastim space filling.[5]

Look at pictures 3. Volume disproportionately occupied by PEG though serupamassa molecule to the protein component. PEG conjugation is an ideal partner to increase hydrodynamic size.[5]

Active substance

Each syringe contains 6 mg pegfilgrastim (Produced in Escherichia coli cells by recombinant DNA technology followed by conjugation with PEG) in 0.6 mL solution for injection. The concentration of pegfilgrastim is 10 mg / mL based on protein alone. The PEG concentration entered is 20 mg / mL.[3]

Excipient substance

- Acetic acid pH 4.
- Sorbitol (E420)
- Polysorbat 20
- Aqua for injecton[3]

Flowchart of Formulation

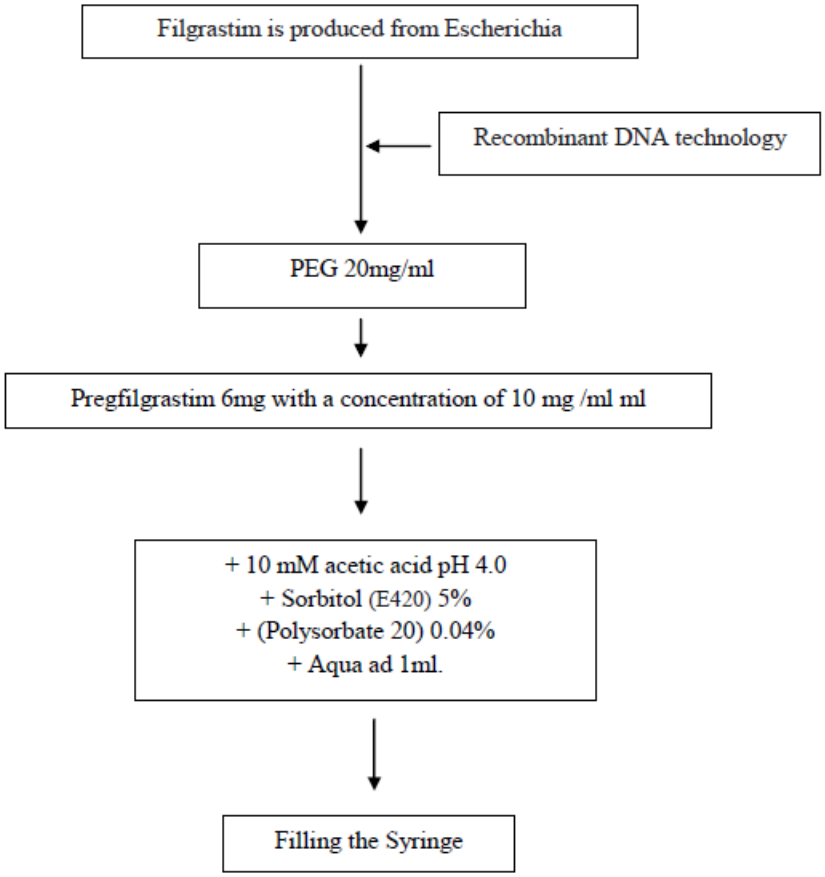

Figure 4: Pregfilgrastim.[2]

Pharmacology

Cancer patients found results that were not linear in the increase and decrease in dosage.[6] The concentration of pegfilgrastim decreased rapidly at the beginning of neutrophil recovery followed by myelosuppressive chemotherapy, besides that body weight was also a factor. Patients with high body weight will increase systemic levels higher than pegfilgrastim after the normal dose is given.[6] Pharmacokinetic parameters of filgrastim in cancer patients after administration subcutaneously is $C_{max:}$: 78.3-175ng / mL, $T_{1/2}$: 25-49 hr AUC_{0-x} : 5640-15-ng.hr/ml, and Clearance 6.68-17.7 mL / hr / kg, with dose of 100µg / kg and 6 mg (single dose).[6]

Faramakokinetik of filgrastim has been studied in healthy volunteers after single intravenous and subcutaneous dose and multiple dose subcutaneous.[1] The first kinetic elimination $t_{1/2}$2.7 h; Vd162 mL / kg; clearance of 0.6 mL / min / kg.[7]

Clinical use

To reduce the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs. Dose is given 6 mg, for children or adults with small stature (weighing less than 45 kg).[6] Use should be no more than 14 days.[6]

a. Place in pharmacotherapy

Hematopoietic colony-stimulating factors (CSFs) such as granulocyte CSF (G-CSF; fi lgrastim), pegylatedG-CSF (peg fi lgrastim), or granulocyte-macrophage CSF (GM-CSF; sargramostim) are important adjuncts in Cancer Patients.[8] Studies in Cancer Patients receiving myelosuppressive or myeloablative chemotherapy have demonstrated that concurrent use of the CSFs can reduce the duration of neutropenia.[8] Hematopoietic growth factors (more speci fi cally G-CSF [filgrastim] or pegylated G-CSF [peg fi lgrastim]) reduce the risk of chemotherapy-induced febrile neutropenia.[8] Granulocyte-colony stimulating factors (G-CSFs), such as filgrastim and pegfilgrastim, may be used as primary or secondary prophylaxis to reduce the risk of FN in Patients receiving myelosuppressive chemotherapy.[8]

Prophylactic administration of CSFs can be used to reduce the myelosuppressive effects of cytotoxic chemotherapy.[8] Three CSFs-granulocyte colony-stimulating factor (G-CSF [filgrastim]), granulocyte-macrophagecolony-stimulating factor (GM-CSF [sargramostim]), and a pegylated long-acting form of filgrastim, pegfilgrastim-are available in the United States.[8] Reviews These products were approved by the US Food and Drug Administration (FDA) to Enhance neutrophil recovery after chemotherapy.[8] Pegfilgrastim was developed with the aim of providing the same pharmacologic bene fi t as fi lgrastim while offering the advantage and convenience of fewer injections.[8]

Pegfilgrastim is a pegylated derivative of filgrastim, leading to a slower release and sustained elevation of neutrophils for up to 14 days.[9] In solid tumors or malignant lymphomas, Several meta-analyzes revealed that prophylactic administration of G-CSFs (filgrastim or lenograstim) after chemotherapy Effectively reduced the frequency of febrile neutropenia and documented infections.[9] However, it is unclear whether pegfilgrastim reduces the occurrence of leukopenia or infectious complications in glioma Patients treated with chemotherapy.[9]

b. Adverse effect

Table 1. Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Filgrastim as Comparator

Body System and Preferred Term	NEULASTA (pegfilgrastim) (n = 465)	Filgrastim (n = 331)
Application Site		
Injection Site Pain	16 (3%)	9 (3%)
Body as a whole		
Pain	8 (2%)	4 (1%)
Chest Pain (Non-Cardiac)	4 (1%)	3 (1%)
Edema Periorbital	3 (1%)	0 (0%)
Fever	3 (1%)	4 (1%)
CNS/PNS		
Headache	20 (4%)	12 (4%)
Musculo-skeletal		
Skeletal Pain	96 (21%)	89 (27%)
Myalgia	32 (7%)	25 (8%)
Arthralgia	27 (6%)	19 (6%)
Back Pain	19 (4%)	26 (8%)
Limb Pain	12 (3%)	7 (2%)
Musculo-Skeletal Pain	5 (1%)	4 (1%)
Neck Pain	4 (1%)	3 (1%)

* Most frequently reported events were considered to be those events reported in ≥ 1% of the patients in the NEULASTA group.

Table 1: Most frequently* reported adverse effect reactions in randomized clinical trials with filgastim as comparator.[10]

Body System and Preferred Term	NEULASTA (pegfilgrastim) (n = 467)	Placebo (n = 461)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (1%)	1 (0%)
Gastrointestinal Disorders		
Diarrhea	9 (2%)	10 (2%)
General Disorders and Administration Site Conditions		
Pyrexia	8 (2%)	9 (2%)
Fatigue	3 (1%)	5 (1%)
Infections and Infestations		
Influenza	6 (1%)	5 (1%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	62 (13%)	41 (9%)
Myalgia	26 (6%)	23 (5%)
Arthralgia	32 (7%)	19 (4%)
Polymyalgia	8 (2%)	7 (2%)
Musculoskeletal Pain	14 (3%)	5 (1%)
Pain in Limb	11 (2%)	5 (1%)
Back Pain	8 (2%)	4 (1%)
Polyarthralgia	5 (1%)	0 (0%)
Nervous System Disorders		
Headache	6 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	8 (2%)	9 (2%)

* Most frequently reported events were considered to be those events reported in ≥ 1% of the patients in the NEULASTA group.

Table 2: Most frequently* reported adverse effect reactions in randomized clinical trials with placebo as control.[10]

Biosimiliars

Biosimilar according to the World Health Organization (WHO) is a term used for biological drugs that have characteristics similar to approved biological drugs (originators) or can be made when the originator's drug patent period is up, but not identical. These similarities include regulation, production processes, quality, safety, purity and potential or efficacy.[11] Biosimilar can be recombinant therapeutic proteins, hormones and antibodies.[11]

Table 3 Summary of the characteristics and studies of PEGylated granulocyte colony-stimulating factors

Name	G-CSF backbone	PEGylation site and composition	Non-clinical activity	Clinical activity
Pegfilgrastim	Filgrastim	Single linear 20 kDa PEG attached to N-terminus methionine of filgrastim	After IV injection of 5 or 100 μg/kg doses, the plasma AUC values for pegfilgrastim were 300 and 550 % higher, respectively, than filgrastim. PK profiles of pegfilgrastim were similar between sham-operated and nephrectomized rats Neutrophil counts in mice increased for 5 days by a single dose of pegfilgrastim (1000 μg/kg, SC) vs. 1–2 days by equiv. dose filgrastim (5000 μg/kg, SC). Duration of chemotherapy-induced neutropenia was 2 days with a single dose of pegfilgrastim (1000 μg/kg SC) and daily doses of filgrastim (300 μg/kg SC)	Breast cancer: Pegfilgrastim (6 mg), $n = 77$ Filgrastim (5 μg/kg/day), $n = 75$ FN incidence 13 vs. 20 %; $p = NS^a$ Breast cancer: Pegfilgrastim (6 mg), $n = 463$ Placebo, $n = 465$ FN incidence 1 vs. 17 %; $p < 0.001$ Colorectal cancer: Pegfilgrastim (6 mg), $n = 123$ Placebo, $n = 118$ FN incidence 2 vs. 8 %; $p = 0.04^b$
Lipegfilgrastim	Filgrastim (XM21)	Single 20 kDa PEG at Thr 134 (natural glycosylation site of G-CSF)	Plasma elimination half-life in monkeys after single 100 μg/kg SC injection was 10.5 h for lipegfilgrastim vs. 10.6 h for pegfilgrastim Comparable PDs with pegfilgrastim in a rat model of cyclophosphamide-induced neutropenia and in monkeys	Breast cancer: Lipegfilgrastim (6 mg), $n = 101$ Pegfilgrastim (6 mg), $n = 101$ FN incidence: 1 vs. 3 %; $p = NS^a$ Lung cancer: Lipegfilgrastim 6 mg, $n = 250$ Placebo, $n = 125$ FN incidence cycle 1: 2.4 vs. 5.6 %; $p = 0.1151$
Ro 25-8315	Nartograstim (KW-2228/ ND-28) Mutant G-CSF with replacement of 5 amino acids at the N-terminal	PEG added to N-terminus and lysine residues: 1–3 units of 20 kDa PEG per G-CSF	Plasma concentration in mice 24 h after injection of 10 μg SC was 110 ng/mL for PEG–ND-28 vs. 6 ng/mL for ND-28 Increased and prolonged neutrophil response in mice with PEG–nartograstim vs. nartograstim; molecules with more PEG units elicited greater neutrophil responses	Breast cancer: Ro 25-8315 (20; 60; 100 μg/kg), $n = 9; 9; 10$ Filgrastim (5 μg/kg/day), $n = 8$ FN incidence: 0 vs. 11 vs. 10 vs. 0 %^{c}
Empegfilgrastim (BCD-017)	Filgrastim	Single 30 kDa PEG	Not reported	Breast cancer: BCD-017 (3 mg; 6 mg), $n = 21; n = 20$ Filgrastim (5 μg/kg/day), $n = 19$ FN incidence: 5 vs. 5 vs. 0 %^{a}

Table 3 continued

Name	G-CSF backbone	PEGylation site and composition	Non-clinical activity	Clinical activity
Maxy-G34	G-CSF modified with 5 amino acid substitutions: removal of potential PEGylation sites (K16R, K34R, K40R) and addition of new PEGylation sites (T105 K, S159 K)	3 units of 5 kDa PEG per G-CSF linked to unique sites resulting from amino acid substitutions	In cyclophosphamide-treated rats, pegfilgrastim had higher specific degradation and bioavailability, and lower distribution volume than Maxy-G34. There were no differences in ANC recovery	Breast cancer: Maxy-G34 (10; 30; 45; 60; 100 μg/kg), $n = 6; 6; 6; 6; 3$ Pegfilgrastim (6 mg), $n = 8$ FN incidence 2.6 vs. 4.2 %^{a}
PEG-rHuG-CSF	Filgrastim	PEG added to N-terminus and 4 lysine residues Filgrastim is mixed with 4.5 or 10 kDa PEG units to produce species with different molecular weights	Increased neutrophil counts in mice and longer serum half-life in rats for PEGylated vs. filgrastim; greater increase with larger PEG units	Not reported
BK0026	Filgrastim	Single 20 kDa PEG conjugated to glutamine 135	Plasma half-life in rats was 7.4 h for BK0026 vs. 8.9 h for pegfilgrastim	Not reported

Table 3: Summery of characteristic and studies of pegylated granulocyte colony-stimullating factors.[12]

Use in indonesia

Name : Neulastim Syringe[13]

Contents : Pegfilgrastim 6 mg 0.6 mL (10 mg / mL) solution for injection[13]

Dosage forms : Injection[13]

Indication : Reducing the duration of neutropenia (decrease in white blood cell count of neutrophils in the blood) and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for non-myeloid malignancies.[13]

Packaging : Prefilled syringe 6 mg / 0.6ml x 1 seed[13]

Dose : 0.5 MU / kg body weight / day.[13]

1 vial 30 MU / ml can be given to patients with a body weight of 60 kg / day.[13]

Dosage can be increased with an increase of 0.5 MU / kg body weight per cycle of chemotherapy.[13]

Giving old : Given for 2 weeks.[13]

Sign in Insurance : Not included in the insurance BPJS.[13]

Drug stability : Stable kept for 24 Months[13]

Storage : At 2-8 Temperature ^{0}C[13]

Product image

CONCLUTION

In the normal individual G-CSF (granulosa Colony Stimulating Factor) will be stimulated normally. While in cancer patients, cancer drugs can reduce the consumption of G-CSF. While filgrastim can serve to help improve G-CSF. In combination with PEG formula Filgrastim (being Pegfilgrastim) will further improve the stimulator of GCF.

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