

# 生物相似藥選用之考量 學術研究 & 臨床想法



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## Outline

- 1 生物相似藥(Biosimilar)是什麼？  
為何biosimilar switching studies重要？
- 2 學術文獻匯集，以G-CSF為例：  
學術 inform 臨床，臨床 reflect 學術
- 3 深入細節看看台灣自己的資料：Effectiveness and Safety of Originator and Biosimilar G-CSF as Primary Prophylaxis in DLBCL
- 4 破解反安慰劑效應，生物相似藥與原廠藥的進用、併存與開立原則

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## Biosimilar & Biosimilar Switching Studies

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## What is biosimilar?

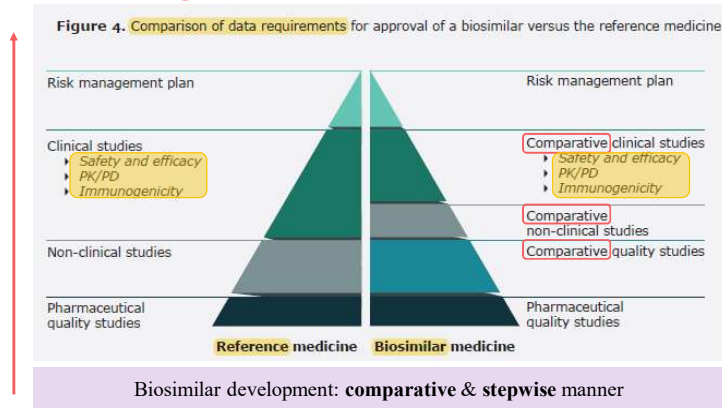
- 1 **High similarity** -  
structure, biological activity & efficacy, safety & immunogenicity.
- 2 The EU approved the first biosimilar in 2006. (Omnitrope)
- 3 **Natural variability** is inherent to all biological medicines.  
Minor differences are **not clinically meaningful**, i.e. no differences are expected in safety and efficacy.
- 4 The EU monitoring system has not identified any relevant difference in the **nature, severity or frequency of adverse effects** between biosimilars and their reference medicines.



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## Biosimilar vs. Originator 不同

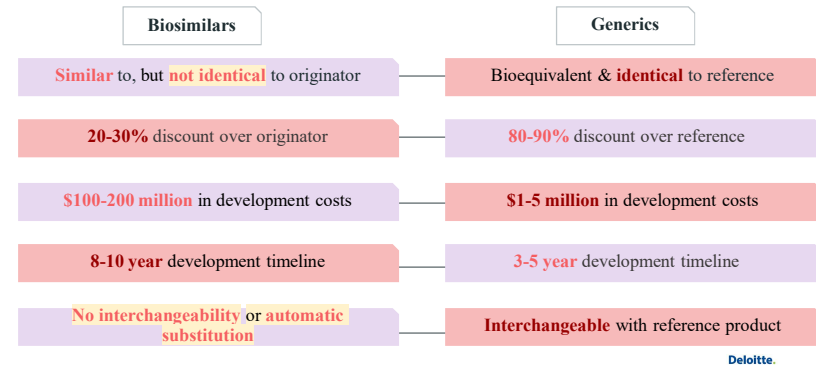
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Biosimilars in the EU. Prepared jointly by the European Medicines Agency and the European Commission

## Biosimilar vs. Generics 不同

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Winning with biosimilars  
Opportunities in global markets

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**FDA U.S. FOOD & DRUG ADMINISTRATION**    Purple Book Glossary    Search

Database last updated: August 22, 2023

### Purple Book

#### Database of Licensed Biological Products

The **Purple Book** Database contains information on all FDA-licensed (approved): **Biological** products regulated by the **Center for Drug Evaluation and Research (CDER)**, including licensed biosimilar and **interchangeable** products, and their reference products.

<https://purplebooksearch.fda.gov/>

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Cyltezo (Adalimumab-adbm)	August 2017	Humira (adalimumab)	<a href="#">Cyltezo information</a>
Renflexis (Infliximab-abda)	May 2017	Remicade (Infliximab)	<a href="#">Renflexis information</a>
Amjevita (Adalimumab-atto)	September 2016	Humira (adalimumab)	<a href="#">Amjevita information</a> Press Release: <a href="#">FDA approves Amjevita</a>
Erelzi (Etanercept-szss)	August 2016	Enbrel (etanercept)	<a href="#">Erelzi information</a> Press Release: <a href="#">FDA approves Erelzi</a>
Inflectra (Infliximab-dyyb)	April 2016	Remicade (Infliximab)	<a href="#">Inflectra information</a> Press Release: <a href="#">FDA approves Inflectra</a>
Zarxio (Filgrastim-sndz)	March 2015	<b>Neupogen (filgrastim)</b>	<a href="#">Zarxio information</a>
	Filgrastim	Neutropenia, neutrophil recovery	3    3    Neupogen/Amgen
	Pegfilgrastim	Febrile neutropenia, acute myelosuppressive radiation exposure	6    6    Neulasta/Amgen
			<b>Approved</b> <b>Launched</b>
Rituximab	Non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis		3    3    Rituxan/Biogen-Genentech
			<b>Approved</b> <b>Launched</b>

<https://www.fda.gov/drugs/biosimilars/biosimilar-product-information>

This page was last updated July 18, 2023

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European Union

Total Approved: 75

Nonproprietary Drug Name	Therapeutic Areas	Approved Biosimilars	Originator/ Company
Filgrastim	Neutropenia, hematopoietic stem cell transplantation, cancer	2	Neupogen/Amgen
Pegfilgrastim	Neutropenia, cancer	8	Neulasta/Amgen
Rituximab	Non-Hodgkin lymphoma, rheumatoid arthritis, B-cell chronic lymphocytic leukemia	5	MabThera/Genentech (Roche)

數量 (態度)  
EU > US<https://www.centerforbiosimilars.com/biosimilar-approvals>

Approved biosimilars may **not** be interchangeable without specific **FDA** designation.

**EU** approved, yet the decision on interchangeability & substitution is made by individual member states.

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「生物相似藥」vs. 「可互換 (interchangeable) 生物相似藥」

最大的不同在

可互換生物相似藥需進行 **switching studies** ,

提供更多 **臨床試驗數據** 證明

此生物相似藥替代原廠藥物的有效性與安全性相同。

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1 Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with **rituximab** in patients with previously untreated **advanced-stage** follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial



2 Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with **rituximab** in patients with previously untreated **low-tumour-burden** follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial

**Comparable.**  
**Biosimilarity proved & approved.**  
[Lancet Haematol. 2017 Aug;4(8):e362-e373.]  
[Lancet Haematol. 2018 Nov;5(11):e543-e553.]

Truxima 可用於 1st-line all-staged **follicular lymphoma**,  
**not indicated** as part of an induction therapy for **DLBCL** patients,  
但是臨床使用 **off-label** 外推性 **OK!**

<https://info.fda.gov.tw/MLMS/H0001D.aspx?Type=Lic&LicId=60001094>



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生物相似性藥品通常只做一個適應症的臨床比較性試驗，但可外推至其他適應症，其中的法規科學原理為：

當生物相似性藥品已確立其與參考藥品之療效並「不具臨床意義的差異」後，對於增加參考藥品之其他適應症，法規單位接受適應症外推的方式，以**避免不必要而重複的臨床試驗**。

適應症外推，必須考量不同適應症所涉及的作用機轉是否相同、免疫原性、不同族群使用之安全性等。因此，生物相似性藥品廠商提供合乎邏輯的證據佐證，根據整體的證據加上外推合理性論述，**經審查單位確認適當且安全無虞後，才可適應症外推**。如推論有困難，應提供額外的臨床比較性試驗證明。

[https://tsrap.org.tw/medicine\\_detail.php?id=529](https://tsrap.org.tw/medicine_detail.php?id=529)



CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial

Equivalent **efficacy** to trastuzumab originator; besides, rate of **adverse events** were similar. Biosimilarity proved and approved as an adjuvant anti-cancer agent for HER2-positive early-stage cancer.

[Lancet Oncol. 2017 Jul;18(7):917-928.]

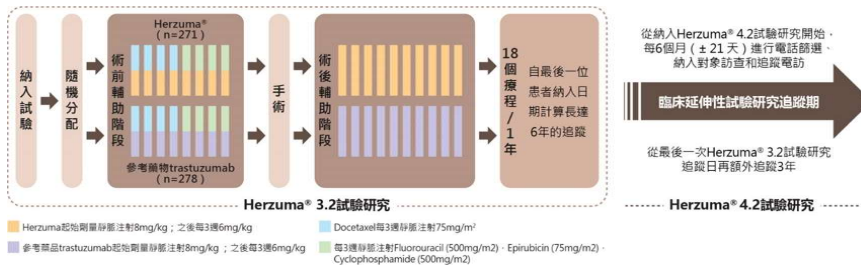


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### 第三期臨床延伸性試驗研究設計 (neoadjuvant & adjuvant)

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- 一項第III期、雙盲、隨機分配、平行分組的對照試驗
- 針對Herzuma® 3.2試驗研究中完成末次隨訪的患者進行多中心、**觀察性**、6年追蹤研究



Primary endpoints: 在罹患HER2陽性早期乳癌(EBC)的病患中，探討Herzuma®相較於參考藥品 trastuzumab作為手術前輔助治療與手術後輔助性治療，以DFS、OS評估Herzuma長期療效。

CI, confidence interval; DCIS, ductal carcinoma in situ; HER2, Human Epidermal Growth factor Receptor-2; LVEF, left ventricular ejection fraction; pCR, pathological complete response; RECIST, response evaluation criteria in solid tumours

### 使用 Herzuma 6年的臨床延伸性試驗療效 長期療效與安全性指標

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	ITT (意圖治療組)		ITT - E (意圖治療延伸組)	
	Herzuma (N=271)	參考藥物 Trastuzumab (N=278)	Herzuma (N=107)	參考藥物 Trastuzumab (N=109)
無疾病存活率 (DFS)				
5年 (95% CI)	0.79 (0.72 – 0.84)	0.81 (0.75 – 0.86)	0.88 (0.80 – 0.93)	0.89 (0.81 – 0.94)
6年 (95% CI)	0.78 (0.71 – 0.83)	0.81 (0.75 – 0.86)	0.87 (0.78 – 0.92)	0.89 (0.81 – 0.94)
HR (95% CI)	1.18 (0.77, 1.80)		1.07 (0.50, 2.32)	
整體存活率 (OS)				
5年 (95% CI)	0.91 (0.86 – 0.94)	0.90 (0.85 – 0.94)	0.98 (0.93 – 1.00)	0.97 (0.92 – 0.99)
6年 (95% CI)	0.89 (0.84 – 0.93)	0.87 (0.81 – 0.91)	0.96 (0.90 – 0.99)	0.94(0.87 – 0.97)
HR (95% CI)	0.95 (0.53, 1.68)		0.59 (0.17, 2.02)	
無惡化存活率 (FFS)				
5年 (95% CI)	0.79 (0.73–0.84)	0.81 (0.75–0.86)	0.91 (0.83–0.95)	0.91 (0.83–0.95)
6年 (95% CI)	0.76 (0.69–0.81)	0.80 (0.73–0.85)	0.87 (0.78–0.92)	0.89 (0.82–0.94)
HR (95% CI)	1.25 (0.84–1.87)		1.08 (0.50–2.34)	

Herzuma具良好耐受性且不良事件(AE、LVEF變化)、免疫原性與參考藥物trastuzumab比例相當。

CI, confidence interval; DCIS, ductal carcinoma in situ; HER2, Human Epidermal Growth factor Receptor-2; LVEF, left ventricular ejection fraction; pCR, pathological complete response; RECIST, response evaluation criteria in solid tumours

## 先進國家推動biosimilar鼓勵政策與策略

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強制轉換	挪威：醫院強制統一採購，低價藥得標後列入處方選項中。 加拿大：特定適應症強制轉換，biosimilar列為新病人處方項目。
處方獎勵	英國：醫師開立單一成分biosimilar達標後可有藥品1%合約價格獎勵。* 新病人90%、舊病人80% 日本：醫師衛教且開立biosimilar，每次可得1500日圓獎勵。
簡化流程	澳洲：事前審查作業簡化。
替代獎勵	澳洲：鼓勵但不強制醫師開立biosimilar於新病人。
收益共享	英國：地方臨床委任小組與醫院收益共享，醫院可保留處方較低價的藥品所節省的成本之固定百分比。

台灣醫藥品法規學會生物相似藥品政策建言  
https://tarap.org.tw/medicine\_detail.php?id=516

## Biosimilar 問世後，使用量的改變？

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## Filgrastim

physicians may be more able and/or willing to adhere to guidelines

→ improved patient outcomes

[Support Care Cancer. 2013;21:2925–32., JAMA Oncol. 2018;4:1779.]



## Infliximab



整體使用量  
原廠藥價位



Inconsistent consumption and price changes

[BioDrugs 2023;37(3):409–20.]

## Biosimilar 問世後，使用量的改變？

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	2017	2018	2019	2020	2021	2022
<b>Filgrastim</b>						
75 mg	16,931	14,863	13,386	15,718	13,415	12,586
150 mg	18,820	24,150	22,712	23,362.3	23,266	25,631
300 mg	144,096	155,671	162,308	177,629.5	167,391	173,261
<b>Lenograstim</b>						
100 mg	50,685	54,421	63,472	69,101.5	66,189	66,324
250 mg	68,726	79,272	82,535	88,570	111,651.5	114,596
<b>Pegfilgrastim</b>						
6 mg	1,130	1,309	1,475	1,418	1,438	1,581
年度量	300,388	329,686	345,888	375,799	383,351	393,979

衛生福利部中央健康保險署  
National Health Insurance Administration  
Ministry of Health and Welfare

## 高榮biosimilar品項

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學術文獻匯集，  
以G-CSF為例：  
Originator and  
Biosimilar G-CSF as  
Primary Prophylaxis

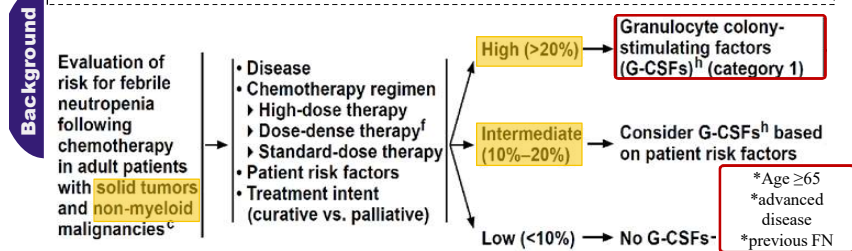
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## Chemotherapy-Induced Neutropenia

ASCO & NCCN:

Prophylactic G-CSF for chemotherapy regimens posing a **high** ( $\geq 20\%$ ) risk of febrile neutropenia.



ASCO, American Society of Clinical Oncology  
NCCN, National Comprehensive Cancer Network

J Natl Compr Canc Netw. 2015 Jan;13(1):e1-7.; NCCN guideline VER 1.2022: Management of Neutropenia, MGF-1;  
J Clin Oncol. 2015 Oct 1;33(28):3199-212. ASCO Practice Guideline Update

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## Approved Biosimilar G-CSF in Taiwan

**Background**

	Formulations	Originator	Biosimilars	Taiwan NHI reimbursement
Short-acting	Filgrastim	Filgrastim (惠爾血添)	Nivestim (奈維血添)	Yes
	Lenograstim	Granocyte (顆球諾得)	None	NA
Long-acting	Pegfilgrastim	Neulasta (倍血添)	Fulphila (福富血)	Yes
			Ziextenzo (血添佐)	Yes

只要approve，就同原廠的給付方式

NHI, National Health Insurance  
NA, not applicable



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## Eligibility Criteria

**Study design** Comparative/observational studies (real-world evidence)

**Method**

### Inclusion criteria

- P** Adult cancer populations ( $\geq 18$  years)
- E** Short-acting G-CSF biosimilar
- C** Short-acting G-CSF originator
- O** Neutropenia incidence

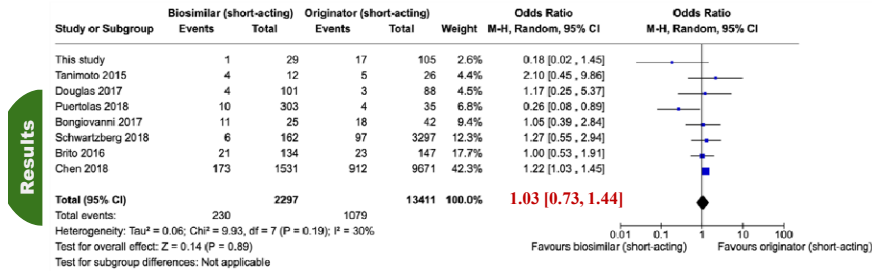
### Exclusion criteria

- P** (1) Populations receiving G-CSF for one of the following purposes:
  - Primary autoimmune neutropenia
  - Hematopoietic stem cell mobilization and engraftment

Under review

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## Forest Plot for Neutropenia Incidence - Short-acting



No statistical difference between the biosimilar and the originator.

Under review

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## Meta-analysis of RCTs - Long-acting



1 comparable efficacy (OR: 0.74, 95% CI: 0.42, 1.30).

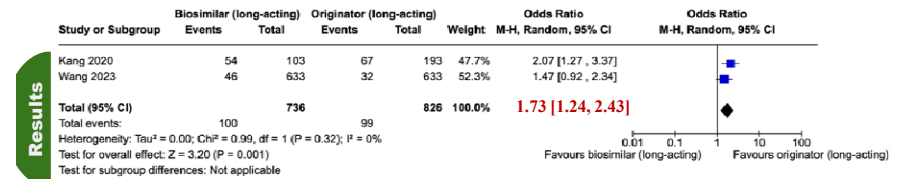
2 A comprehensive review showed similar efficacy in terms of incidence of febrile neutropenia, duration of severe neutropenia, and infection rates.

Kahan Z, et al. BMC Cancer. 2019;19:122.  
Blackwell K, et al. Ann Oncol Off J Eur Soc Med Oncol. 2017;28:2272-7.  
Busca A, et al. Expert Rev Hematol. 2018;11:155-68.

Under review

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## Forest Plot for Neutropenia Incidence - Long-acting



- Long-acting originator G-CSF exhibited a superior effect
- Study 數量過少

Under review

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## Safety outcomes

1 Most reported adverse events associated with G-CSF use include pyrexia, bone and muscle pain, fatigue, rash, and leukocytosis.

2 Similar to existing literature

3 Serious adverse events (e.g., pulmonary embolism, hypertensive crisis)



Renner P, et al. Cochrane database Syst Rev. 2012;10:CD007913.

Under review



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## Findings of other literature

	Author (Year)	Cancer type	G-CSF formulation	Efficacy endpoints	Conclusion
Discussion	Botteri 2017	Breast cancer	Long-acting	<ul style="list-style-type: none"> <li>Duration of severe neutropenia</li> </ul>	<p><b>No significant differences</b> in clinical efficacy and safety between biosimilar and reference G-CSF in breast cancer patients.</p>
	Yang 2019	Unrestricted	Short-acting	<ul style="list-style-type: none"> <li>FN incidence in cycle 1</li> <li>Duration of severe neutropenia in cycle 1</li> <li>Time to ANC recovery</li> </ul>	<p><b>Existing evidence suggests highly comparable efficacy and safety profiles</b> for supportive care biosimilars and their reference biologics in oncology.</p>

Eur J Cancer. 2018 Jan;89:49-55; ; BioDrugs. 2019 Oct;33(5):589-594.

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## Routes of administration

The banner includes the following claims and presentations (emphasis original):

- "In a Real-World Study with nearly 11,000 patients Pegfilgrastim **PFS** resulted in a **significantly higher risk of FN** vs. Onpro® (frame 1)
- "Across all cycles of chemotherapy, the incidence of FN associated with prefilled syringe (PFS) was 1.7% (n = 455) vs 1.3% (n = 126) for Neulasta® Onpro® (frame 1)
- A large presentation of an upward arrow containing the claim, "31%\* \*p = 0.01" (frames 1 and 2)
- "With PFS, **FN incidence increased by 31% vs Onpro®** (frame 2)

Prospective cohort study

Incidence of febrile neutropenia


Patients receiving primary prophylactic G-CSF

Variations in **patient adherence**


<https://www.fda.gov/media/150751/download>  
Ritkin RM, et al. Support Care Cancer. 2022;30:7913-22.

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## Routes of administration



Neulasta on-body injector (OBI)  
自動皮下注射装置



Neulasta prefilled syringe (PFS)

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

David Shechter, Ph.D.  
Senior Manager, Regulatory Affairs  
Amgen  
One Amgen Center Drive, Mail Stop 27-4-F  
Thousand Oaks, CA 91320-1799

RE: **BLA 125031**  
**NEULASTA®** (pegfilgrastim) injection, for subcutaneous use  
MA 1706

07/07/2021

202.1(e)(3)(i); 202.1(e)(5). These violations are concerning from a public health perspective because this promotional communication's misleading claims could cause healthcare providers to conclude that Neulasta delivered via the Onpro on-body injector (OBI) is more effective than Neulasta delivered via prefilled syringe (PFS) or that it is more effective than FDA-licensed biosimilar pegfilgrastim products, which are only delivered via PFS.

<https://www.fda.gov/media/150751/download>

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## Observational studies:

**Short-acting biosimilar/originator G-CSF:** comparable effectiveness (OR 1.03; 0.73, 1.44)

**Long-acting originator G-CSF** exhibited a superior effect (OR 1.73; 1.24, 2.43)

## RCTs:

Comparable efficacy (OR 0.74; 0.42, 1.30).



Under review



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深入細節看台灣資料：  
Effectiveness and Safety  
of Originator and  
Biosimilar G-CSF as  
Primary Prophylaxis in  
DLBCL

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## Top-Down Approach: Systematic Change



**Hospital-wide** mandatory  
substitution started in 2020.



**Non-medical switching** -  
no **clinical** justifications for selecting  
biosimilars or originators.

## Background

### Establishing Taiwan's Own Evidence



The clinical effectiveness of biosimilars has been discussed extensively in Europe.



Higher risk of febrile neutropenia in Asians compared to Caucasians.



Lack of RWE in Asia/Taiwan →

We aimed to investigate whether the originator/biosimilar G-CSF differ in febrile neutropenia, infection, incidence and duration of severe neutropenia, and post-chemotherapy nadir ANC.

ANC, absolute neutrophil count

Rheumatology (Oxford). 2022;61:3596-605.; BioDrugs. 2017;31:83-91.;  
Drug Discov Today. 2012;17:63-70.; EMA. Biosimilars in the EU - information guide for healthcare professionals. 2019.

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## Study design

Method	P	Previously untreated patients with DLBCL treated with first-line systemic chemotherapy and primary prophylactic* G-CSF *≤ 3 days of completion of (immuno)chemotherapy	
	E	G-CSF Biosimilars (Nivestim, Fulphila)	G-CSF Originators (Filgrastim, Lenograstim, Neulasta)
		Same G-CSF product should have been used throughout the first cycle to be included.	
	O	Primary Occurrence of febrile neutropenia	Secondary Incidence of severe neutropenia Duration of severe neutropenia Incidence of any infection Any treatment-related AE
	T	From 1 <sup>st</sup> January 2015 to 31 <sup>st</sup> December 2022	
	S	Retrospective cohort study (data from VGHKS EHR)	

AE, adverse events; VGHKS, Kaohsiung Veterans General Hospital, Taiwan; EHR, electronic health records

Under review

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## Multivariable logistic regression for febrile neutropenia

Variable	All G-CSF		Short-acting G-CSF	
	Original	Weighted	Original	Weighted
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Biosimilar vs. originator	0.31 (0.06, 1.61)	0.18 (0.04, 0.91)*	0.23 (0.02, 2.14)	0.16 (0.02, 1.14)
Age (years)	1.06 (1.00, 1.12)*	1.06 (1.02, 1.10)*	1.06 (0.99, 1.13)	1.06 (1.00, 1.11)*
B symptoms	4.39 (1.47, 13.10)*	4.18 (1.33, 13.15)*	4.90 (1.37, 17.56)*	4.14 (1.12, 15.37)*
ECOG PS (≥2 vs. 0-1)			3.94 (1.06, 14.66)*	3.48 (0.93, 12.98)
Ann Arbor stage (ref: stage 1)				
2			9.40 (1.28, 69.26)*	8.90 (1.48, 53.62)*
4	3.75 (1.31, 10.73)*	4.14 (1.44, 11.90)*	15.60 (2.54, 95.91)*	16.18 (3.30, 79.39)*
Overall significance	<0.001	<0.001	<0.001	<0.001

Abbreviation: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony-stimulating factor; OR, odds ratio; ref, reference  
\* statistically significant with  $p < 0.05$

Under review

## Multivariable logistic regression for infection, severe neutropenia, post-chemotherapy nadir ANC

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	Infection				Severe neutropenia				Post-chemotherapy nadir ANC			
	All G-CSF		Short-acting G-CSF		All G-CSF		Short-acting G-CSF		All G-CSF		Short-acting G-CSF	
	Original	Weighted	Original	Weighted	Original	Weighted	Original	Weighted	Original	Weighted	Original	Weighted
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	β (SE)	β (SE)	β (SE)	β (SE)
<b>Biosimilar vs. originator</b>	0.79 (0.23, 2.77)	0.60 (0.18, 2.01)	0.24 (0.03, 2.00)	0.16 (0.02, 1.23)	0.21 (0.04, 1.11)	0.12 (0.02, 0.66)*	0.18 (0.02, 1.66)	0.10 (0.01, 0.80)*	1176.30 (495.27)*	1452.69 (669.13)*	1457.05 (524.37)*	1570.75 (762.89)*
<b>Male vs. female</b>											753.80 (432.30)	886.01 (475.12)
<b>Age (years)</b>					1.07 (1.01, 1.13)*	1.07 (1.02, 1.12)*	1.05 (0.99, 1.12)	1.06 (1.01, 1.12)*				
<b>B symptoms</b>	4.05 (1.55, 10.55)*	3.96 (1.48, 10.60)*	4.15 (1.48, 11.67)*	4.32 (1.53, 12.22)*	3.57 (1.26, 10.07)*	3.55 (1.19, 10.36)*	4.30 (1.31, 14.16)*	4.19 (1.24, 14.16)*				
<b>ECOG PS (≥2 vs. 0-1)</b>	3.16 (1.17, 8.59)*	3.12 (1.13, 8.64)*	2.91 (1.02, 8.36)*	3.02 (1.10, 8.28)*			3.03 (0.85, 10.79)		-815.93 (465.98)			

Under review

## Safety & 結果小結

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**G-CSF discontinuation, deaths:**  
NOT attributable to the use of biosimilar/originator G-CSF.

**Biosimilar vs. Originator**  
RWE效果(clinical effectiveness)相似  
嚴重副作用(severe AEs)也相似/沒有

Under review

1 Our findings regarding **risk factors in Taiwanese patients** align with evidence from predominantly **American and European** populations.

2 Blackwell et al.: mechanisms of filgrastim involve **selective binding** to the G-CSF receptor, a process that **does not differ** across populations.  
→ **Extrapolating** evidence from other **ethnic groups** may be **appropriate**.  
→ Reasonable to generalize findings from **other tumor types**.

Under review

Blackwell K, et al. Ann Oncol. 2015;26:1948-53.

## Experiences beyond Taiwan

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**Japan Society of Clinical Oncology's Guidelines** for the proper use of G-CSF 2013 (ver. 5): **biosimilar filgrastim is recommended** because efficacy and safety of biosimilar filgrastim is **equivalent** to reference filgrastim.

[Lancet Oncol. 2021;22(3):e82.]



**Biosimilar filgrastim** accounted for **7%** of filgrastim users in 2014, which increased to **16%** in 2015 and to **36%** in 2016. The market for biosimilar agents seems to be increasing over time, indicating **broader acceptance** of these drugs.

[JAMA Oncol. 2018;4(12):1779-1781.]

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## Immunogenicity



GUIDELINE

Immunogenicity is **low to nonexistent** with filgrastim biosimilars based on the lack of immunogenicity seen with the originator filgrastim biologics and the nature of filgrastim as an **unglycosylated** protein.

[NCCN. Hematopoietic Growth Factors Version 2.2023. Accessed May 23 2023]



Alternation of G-CSF products, either **between biosimilars** or a **biosimilar and an originator**, did **not raise additional clinically meaningful concerns** with regard to safety including **immunogenicity**.

[Ann Oncol. 2015 Sep;26(9):1948-1953]

Discussion

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## On the other side of evidence...

A retrospective **pharmacovigilance** study using VigiBase® with nearly 30 years of data showed that:

- Grasim®: increased pyrexia, myalgia, and back pain.
- Zarzio®: increased risk of arthralgia and neutropenia.
- Nivestim®: more bone pain.

**Limitation:** retrospective evaluation using code identification

- Unsolvable, significant, **residual confounding**
- Reporting bias** - detailed reporting & recording: **today >> previous years**,  
→ influence the observed associations

Discussion

## Another Factor: Rituximab

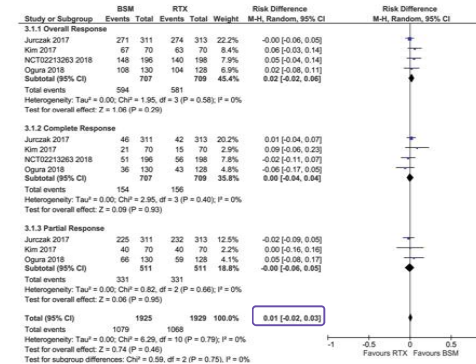


Fig. 5 Forest plots of the response rates of rituximab-biosimilar versus reference in non-Hodgkin's lymphoma. Risk difference values higher than 0 favor biosimilars for the efficacy outcomes. CI confidence interval, M-H Mantel-Haenszel method, NHL non-Hodgkin's lymphoma

**Our assumption:**  
no difference in the  
originator &  
biosimilars of  
rituximab.

Lee, et al. reported no  
difference in  
comparative efficacy  
& safety of rituximab  
biologics.

BioDrugs. 2019;33(5):469-483.

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## Cost-effectiveness analysis

- 1 **Taiwan's NHIRD:** Positive effectiveness and cost-effectiveness results for **primary prophylactic** use of G-CSF in patients with non-Hodgkin's lymphoma.



Primary prophylactic G-CSF effective in:

- Preventing neutropenia with a **74% reduction in incidence**
- Reducing the incidence of **febrile neutropenia by 83%** at an incremental cost of US\$52 per cycle to reduce 1% of febrile neutropenia.

[Wen T-J, et al. J Eval Clin Pract. 2017;23:288-93.]

- 2 **US:** primary prophylaxis is cost-effective, suggesting **expanded use** of prophylactic G-CSF to reduce avoidable hospitalisations.


[Li E, et al. JCO Oncol Pract. 2021;17:e1235-45.]

NHIRD, National Health Insurance Research Database

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**Conclusion**



**No statistically significant differences** between the biosimilar G-CSFs and the originators for patients with DLBCL receiving the first course of chemotherapy.

**Clinically equal effectiveness and safety** of biosimilars and originators is suggested in routine care.

**now future**

1. 健保 - 不是挖東牆補西牆，而是面面俱到的每一面牆
2. 自費 - 可近性提高
1. 臨床醫療端 - Biosimilar **friendliness** ↑
2. 藥委會 - Inform **policy making of procurement**
3. 健保署 - **Refined allocation** of resources
4. 病人 - 各方被照顧，覺得被呵護 🤗

Under review


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*Biosimilar 用過就知道，  
nocebo effect 只是假象*

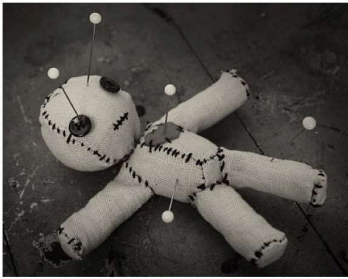
*學術 inform 臨床，臨床 reflect 學術*

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**NOCEBO EFFECT**

a harmless thing that causes harm  
because you believe it's harmful



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*thank you*