Biosimilars are essential for sustainable healthcare systems; however, key challenges remain as seen with long-acting insulin analogues

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ABSTRACT
Sales of medicines continue to grow world-wide driven in part by increasing expenditures on biological medicines leading to concerns with the long-term sustainability of European healthcare systems. The increasing use of biosimilars at lower costs can potentially address this. However, there can be concerns with their prescribing. There are also concerns with biosimilar insulin glargine including concerns with different devices despite increasing sales of long-acting insulin analogues worldwide. Consequently, a need to appraise the European biosimilar market incorporating measures to enhance their use including potential ways to increase the prescribing of biosimilars of insulin glargine at lower costs. Multiple approaches were used to undertake the study including researching measures to enhance biosimilar use and their impact across Europe. In addition, undertake cross national research on the utilization and expenditure of long-acting insulin analogues, which includes biosimilars, principally among Central and Eastern European countries. Multiple demand-side measures across the countries have enhanced the use of biosimilars. There was variable use of biosimilar insulin glargine 100 IU/ml driven by increasing use of patented 300 IU/ml formulations and small price differences between the originator and biosimilars in practice. Overall, multiple demand-side initiatives can appreciably increase biosimilar use benefitting all groups. Additional measures are needed to enhance future prescribing of long-acting biosimilar insulin analogues.

INTRODUCTION
Global expenditure on medicines has risen in recent years. Expenditure of medicines is expected to reach US$1.5 trillion by 2023, which represents an annual compounded growth rate of 3%–6% (IQVIA, 2019a). This increase in expenditure is driven by a number of factors. These include increasing expenditure on biologicals for orphan diseases and cancer, a growing prevalence of non-communicable diseases (NCDs) and changes in clinical practice (Godman et al., 2018a, 2021a). We are aware that approximately one fifth of health care spending in Europe is out-of-pocket, with the proportion greater among those patients with low income (OECD, 2020; Thomson et al., 2019).

High patient co-payments and reimbursement issues with biologic medicines have resulted in many Central and Eastern European (CEE) countries struggling to fund originator biologic medicines (Baumgart et al., 2019; Tubic et al., 2021). Rencz et al. (2015) found only 0.25% of all patients diagnosed with psoriasis were treated with biologics among six researched CEE countries, with a 14.6-fold difference in utilization rates between them (Rencz et al., 2015). There have also been similar disparities with medicines to treat patients with orphan diseases and cancer across Europe (EURODIS, 2018; Hofmarcher et al., 2019). This urgently needs addressing to ensure equitable healthcare for all across Europe, especially with rising rates of NCDs and concerns with unequal funding for priority disease areas such as diabetes (Godman et al., 2018a, 2021b; Mardare et al., 2022).

Biosimilars should be of interest to improve access, affordability, and subsequent care of patients (Cozijnsen et al., 2018; Dutta et al., 2020; Godman, 2021; Jang et al., 2021). Davio (2018) estimated accumulated savings from the increasing use of biosimilar etanercept, infliximab, and rituximab biosimilars in the UK was US$275 million during the 2017 to 2018 fiscal year (Davio, 2018). However, there are concerns with biosimilar use in some countries, which includes issues with their effectiveness and safety (Godman, 2021; Sagonowsky, 2019; Vandenplas et al., 2021). This is reflected by the usage of anti-TNF biosimilars for rheumatology patients ranging from 90% of all anti-TNFs in Denmark by the end of 2016 to just 5% in Belgium and Ireland and 2% in Switzerland (Araújo et al., 2019). Similarly, in another study, their utilization ranged from 0% of total anti-TNFs in Hungary up to 81% in Norway and 96% in Denmark (IQVIA, 2019b).

There have also been issues with administering biosimilars of long-acting insulin analogues among European countries (Chapman et al., 2017; Greener, 2019; Godman et al., 2021c). This is a concern with the costs of diabetes and associated complications reaching up to 2.2% of Gross Domestic Product by 2030 (Bommer et al., 2018). Long-acting insulin analogues were developed to reduce hypoglycemia, including nocturnal hypoglycemia, among patients with diabetes requiring insulin (Rys et al., 2015; Tricco et al., 2021). There have though been concerns regarding their additional costs compared with insulins such as NPH insulins (Caires de Souza et al., 2014; Ewen et al., 2019). However, these extra costs can be offset by savings elsewhere (Godman et al., 2021c; Lee et al., 2020). As a result of these potential cost offsets, coupled with their perceived patient benefits, long-acting insulin analogues have become the most utilized insulin in upper-middle and high-income countries (Ewen et al., 2019). The costs of long-acting insulin analogues can be reduced by the availability of biosimilars (Haque et al., 2021a). However, the originator company has been promoting the patented high concentration 300 IU/ml formulation of insulin glargine (Gla-300) to protect their overall insulin glargine sales as well as reduce the price of 100 IU/ml formulation to reduce the attractiveness of this market for biosimilar manufacturers (Godman et al., 2021b; Tubic et al., 2021).

Consequently, we believe there is a need to consolidate current knowledge regarding measures to enhance biosimilar use and their impact across Europe. In addition, look more closely at the situation with insulin glargine across Europe as the first in class biosimilar given concerns with its initial uptake coupled with the need to conserve resources. The combined findings can be used to guide key stakeholder groups on potential ways in the future to enhance biosimilar utilization, including insulin glargine biosimilars, across Europe and wider. This is seen as vital to encourage greater competition among biosimilar manufacturers to benefit all key stakeholder groups given rising expenditure on medicines and concerns with the need to preserve universal healthcare among European countries. This includes patients with diabetes requiring long-acting insulin analogues where costs and available resources are a concern. We believe these findings can also be of benefit to low- and middle-income countries struggling to finance healthcare for all their citizens in the public sector including patients with diabetes (Godman et al., 2020a, 2020b; Haque et al., 2021b; Mardare et al., 2022).

METHODS
A mixed-method approach was adopted. This included initially a narrative review of published studies regarding
biosimilars, including initiatives that have been used among countries to enhance their use. This was combined with cross national quantitative and qualitative research among European countries, especially CEE countries, regarding their utilization and expenditure on long-acting insulin analogues with a particular focus in insulin glargine and its biosimilars.

Narrative literature review

We undertook a narrative review of published studies. This included documenting the impact of demand-side measures that had been instigated among European countries, including CEE countries, to enhance uptake and prescribing of biosimilars. In addition, studies where there had been limited use of biosimilars and the rationale. We did not undertake a systematic review as there have been previous studies exploring these issues. This includes documenting the efficacy, safety, and immunogenicity of switching between biosimilars and originators, coupled with the key benefits of biosimilars, and we wanted to build on this (Barbier et al., 2020; Bertolani and Jommi, 2020; Dutta et al., 2020; Godman 2021; Godman et al., 2021a, 2021d; Kim et al., 2020). The documented examples are based on the considerable knowledge of the senior level co-authors and subsequently contextualized.

The demand-side measures will be collated under the Education, Engineering, Economics, and Enforcement (4Es) to aid comparisons (Wettermark et al., 2009a). Table 1 provides definitions and examples of the 4Es.

This is similar to approaches that have been used when debating key areas principally from a health authority perspective (Bochenek et al., 2017; Godman et al., 2018a, 2021a, 2021e, 2021f, 2021g; MacBride-Stewart et al., 2021).

Cross national drug utilization and expenditure study

This study principally concentrated on CEE countries given concerns with the utilization and funding of higher price biological medicines in these countries (Baumgart et al., 2019).

The CEE countries chosen for this study provide an extensive range based on their population size, geography and economic power (Godman et al., 2019a). We also included three high income Western European countries and regions for comparison purposes. These were Italy, Spain (Catalonia), and the UK (Scotland); chosen as the health authorities in these countries have instigated multiple measures to enhance the prescribing of biosimilars (discussed in Table 2). We limited Western European countries to these three as the main focus of this paper was on CEE countries.

Heath insurance company and health authority databases were principally interrogated from 2014 or later until 2020 to determine pricing, expenditure, and utilization patterns principally for the different insulin glargine preparations. These databases were chosen as they are seen as robust and are audited regularly (Godman et al., 2019a, 2019b, 2021b; Vogler and Schneider, 2019). The findings were used to determine changes in utilization patterns for long-acting insulin analogues during the study period as well as changes in the utilization of biosimilars of insulin glargine during the study period. In addition, price changes for both originator and biosimilar insulin glargine over time.

Defined daily doses (DDDs) were used where possible for utilization to enhance the comparisons between countries, with DDDs recognized as a robust measure for undertaking cross-country utilization research (Godman et al., 2014, 2021f, 2021h; Tubic et al., 2021).

Principally reimbursed pricing and expenditure data was used as the perspective of this paper is that of health authorities. This approach has been used before to provide comparisons between European countries (Godman et al., 2014, 2019a). Expenditure data remained in the local currency where relevant in order to avoid potential biases due to currency fluctuations. This is because we were principally interested in percentage differences over time for both the biosimilars and originators, as well as any price reductions for both of them over time, rather than absolute pricing levels.

Qualitative research regarding insulin utilization patterns

The senior-level co-authors from each of the studied countries were approached to provide feedback regarding the possible rationale for the insulin utilization and expenditure patterns seen. They were also approached to provide guidance on possible next steps that could be instigated among European countries to enhance savings from the increased use of biosimilars. We have used similar approaches in the previous publications (Bochenek et al., 2017; Godman et al., 2019a, 2021a, 2021e, 2021f, 2021g, 2021h; Haque et al., 2021b).

We did not seek ethical approval for this study as we were not dealing directly with patients. This is in agreement with national legislation and institutional guidelines. In addition, endorsed in previous publications which have involved the co-authors (Godman et al., 2019a, 2021b; Hesse et al., 2013, Tubic et al., 2021).

RESULTS

We will first document initiatives regarding biosimilars and their impact before discussing the patterns seen regarding utilization and expenditure for long-acting insulins, including biosimilars, during the study period.

Initiatives to enhance the utilization of biosimilars and their impact

Table 2 documents the wide range of demand-side measures that have introduced by different European countries and their influence collated under the 4Es.

Long-acting insulin analogues including insulin glargine

Utilization and expenditure patterns

There has typically been growing expenditure and utilization of long-acting insulin analogues as a percentage of total insulins among the European countries included in this study (Figs. 1 and 2). The greatest increase in utilization among CEE countries was seen in Poland; however, this was from a low base. By 2020, the highest percentage utilization of long-acting insulin analogues among the studied European countries was seen in Estonia (56.5% of total insulins) followed by B & H (35.5%). There was also considerable usage in Catalonia at 55.2% of total utilization.

There were similar findings when comparing the change in percentage expenditure on long-acting insulin analogues versus total expenditure on insulins during the study period (Fig. 2). However, typically a greater percentage reflecting higher acquisition costs for insulin analogues despite price reductions.
### Table 1. Explanation and examples of health authority activities to influence medicine utilization—4Es.

| Activity and explanation                                                                 | Examples                                                                                                                                                                                                 |
|------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Educational activities—includes formularies and prescribing guidance                       | • National and regional formularies including the “Wise List” in Stockholm County Council and the WHO Essential Medicine List (Gustafsson et al., 2011; Perumal-Pillay and Suleman, 2017; Matlala et al., 2020) |
|                                                                                         | • Prescribing guidance (national, regional, or local) for physicians in hospitals and ambulatory care including activities by Drug and Therapeutic Committees as well as community pharmacists (Lima-Dellamora Eda et al., 2014; Marković-Peković et al., 2017; MashaBa et al., 2019) |
|                                                                                         | • Education of key stakeholder groups concerning all aspects of biosimilars including regulations for their marketing authorisation to help dispel myths (Godman et al., 2021a; Moorkens et al., 2017) |
|                                                                                         | • Prescribing targets, e.g., % of biosimilars prescribed (Godman et al., 2021a; MacBride-Stewart et al., 2021; NHS Scotland, 2018)                                                                            |
|                                                                                         | • Percentage (%) adherence to agreed guidelines (Matsite et al., 2017; Niaz et al., 2019; Sefah et al., 2021)                                                                                                 |
| Engineering activities—includes managerial interventions such as quality targets for prescribing as well as price: volume agreements | • Price: volume agreements in ambulatory care to keep expenditures for medicines within agreed spending limits (Adamski et al., 2010)                                                                     |
|                                                                                         | • WHO criteria for assessing the quality of prescribing in ambulatory care, especially among low- and middle-income countries (Niaz et al., 2019; Nyabuti et al., 2020)   |
|                                                                                         | • Introduction of formalized processes to improve the managed entry of new medicines to help maximize available resources as well as improve the quality of care provided (Eriksson et al., 2017; Godman et al., 2015, 2021a) |
|                                                                                         | • Financial incentives for hospitals and physicians with prescribing an agreed list of medicines and/ or reaching agreed prescribing targets (Wettermark et al., 2009b; Martin et al., 2014; MacBride-Stewart et al., 2021) |
| Economic interventions—includes financial incentives for physicians and higher co-payments for more expensive products than the current reference molecules | • Economic incentives for GPs in the UK to meet agreed quality targets (Quality and Outcomes Framework) (Sutcliffe et al., 2012; Leporowski et al., 2018) |
|                                                                                         | • Higher co-payments for patients wishing originators versus generics where applicable or patented medicines when multiple sourced medicines are available in the class (Brill, 2020; Godman et al., 2013; Hesse et al., 2013) |
|                                                                                         | • Potential for shared savings with increasing use of biosimilars                                                                                                                                    |
|                                                                                         | • Delisting of medicines from reimbursement lists due to concerns with their effectiveness and/ or value (Hesse et al., 2013; Parkinson et al., 2015)                                                |
|                                                                                         | • Compulsory prescribing restrictions for medicines when concerns with their value (Godman et al., 2013, Voucina et al., 2011). These include prescribing restrictions for originator biological medicines versus biosimilars for patients with rheumatoid arthritis in Denmark and Norway (Araújo et al., 2019) |
|                                                                                         | • Compulsory INN prescribing or compulsory generic substitution apart from a minority of identified medicines and situations including GPs writing no substitution on prescriptions (Garuoliene et al., 2011; Godman et al., 2009, 2021a; South Africa Pharmacy Council, 2020) |
| Enforcement—includes regulations by law such as prescribing restrictions                  | • Introducing laws for pharmacists to reduce or negate the selling antibiotics without a prescription (Godman et al., 2021a; Jacobs et al., 2019)                                                            |

NB: INN = International Non-proprietary Name; WHO = World Health Organization.

We also saw a considerable variation in the prescribing of biosimilar insulin glargine compared with total insulin glargine across Europe (Fig. 3).

**Rationale for differences in utilization and expenditure patterns**

The differences in the utilization patterns for biosimilar insulin glargine (Fig. 2) have in part been driven by the originator company promoting patented Gla-300 as well as lowering the price of originator 100 IU/ml (Table 3) to compete. These combined activities alongside limited demand-side measures (Table 4) have been successful with no biosimilar 100 IU/ml insulin glargine launched to date in Albania or Latvia as well as limited use in Bulgaria, B & H, Estonia, Romania, and Slovenia.

These findings of limited or no use of biosimilars to date contrast with growing utilization of biosimilar insulin glargine in the other studied European countries, i.e., Lithuania, Hungary, Poland, and Scotland, with the greatest utilization seen in Poland.

Table 3 documents price changes over time of the different insulin glargine preparations (100 IU/ml) among the studied countries.

Table 4 provides a summary of the rationale for the changes seen in Figures 1–3 as well as Table 3.

**DISCUSSION AND THE IMPLICATIONS**

We will break the discussion down into the implications of the findings for the biosimilar market in general and subsequently
Table 2. The extent of demand-side measures that have been instigated influence biosimilar use among European countries and their impact where known [adapted from (Godman et al., 2021a, 2020c; Godman, 2021; Kim et al., 2020)]

| Country/ Region | Details of the initiatives | Influence/ outcome where known |
|-----------------|----------------------------|--------------------------------|
| **Belgium—various biosimilars**<sup>1</sup> (Vandenplas et al., 2021) | *Education and Economics*<sup>2</sup> | - Market share of biosimilar adalimumab and etanercept in 2019 was 5.2% and 12.5%, respectively, of the reference product—greater for infliximab (43.7%)<sup>3</sup> |
| Bosnia and Herzegovina (B & H) (Tubic et al., 2021) | *Education* | - The market share of biosimilar trastuzumab and rituximab were 8.5% to 12.7% of their respective IV formulations in 2019<sup>3</sup> |
| Catalonia—Spain | *Education:*<sup>2</sup> | - The market share of biosimilar insulin glargine (100 IU/ml) was only 5.0% of total insulin glargine (100 IU/ml) utilization in 2019 with the 300 IU/ml insulin glargine (patented) formulation accounting for 47.0% of total insulin glargine in 2019<sup>3</sup> |
| **Denmark—Adalimumab**<sup>4</sup> (Jensen et al., 2020) | *Engineering:*<sup>5</sup> | - Very limited use of biosimilar adalimumab, infliximab, rituximab and trastuzumab in recent years exacerbated by limited attractiveness of the biosimilar market<sup>3</sup> |
| | *Economic incentives:*<sup>5</sup> | - This is despite a reduction of 64% in the price of biosimilar infliximab versus the originator in recent years<sup>3</sup> |
| | *Engineering:*<sup>5</sup> | - The overall utilization of the different biosimilars was influenced by the extent and nature of contracts with originator companies as seen with adalimumab<sup>3</sup> |
| | *Enforcement:*<sup>5</sup> | - 3 biosimilars won the adalimumab tender among the hospitals in Denmark—resulting in one biosimilar being prescribed for children and two biosimilars for adults depending on the Region in Denmark<sup>3</sup> |
| | *Economics:*<sup>5</sup> | - The proportion of adalimumab biosimilars versus total adalimumab increased from 71.6% in November 2018 to 95.1% by December 2018<sup>3</sup> |
| | *Engineering:*<sup>5</sup> | - Expenditure on adalimumab decreased by 82.8% from September 2018 to December 2018 among hospitals in Denmark<sup>3</sup> |

<sup>1</sup> Limited educational initiatives from the health authorities, e.g., no counter-action to increased promotion and use of still patented biologicals where possible including 300 IU/ml versus 100 IU/ml insulin glargine

<sup>2</sup> Mandated price reductions for both the originator and biosimilars following patent loss—resulting in similar prices for the biosimilars and originators in practice and limited further price reductions of biosimilars in ambulatory care without volume guarantees

<sup>3</sup> Lack of transparency of price reductions in practice especially in hospitals

<sup>4</sup> Currently a lack of educational initiatives among the authorities in B & H to address concerns and trust among physicians and patients with biosimilars alongside a general lack of demand-side measures instigated by the authorities to enhance the preferential prescribing of biosimilars versus the originators

<sup>5</sup> Key issues including substitutability and interchangeability have currently not been clearly defined by the State regulatory authority, the Agency for Medicinal Products and Medicinal Devices of B & H

<sup>6</sup> Workshops, meetings, and materials prepared by the Catalan Health System including the rationale for biosimilars, key concepts and recommendations, and distributed to healthcare professionals and patients

<sup>7</sup> Prioritization of biosimilars where feasible in guidelines and formularies

<sup>8</sup> Education:

<sup>9</sup> Engineering:

<sup>10</sup> Economic incentives:

<sup>11</sup> Variable bonuses to physicians linked to indicators

<sup>12</sup> Potential penalties for exceeding budget goals especially if key indicators are missed

<sup>13</sup> Increasingly aggressive contracting with companies to enhance savings from biosimilar availability

<sup>14</sup> Engineering:

<sup>15</sup> Single purchaser of medicines for all hospitals in Denmark (achieving economies of scale)

<sup>16</sup> Choice of biological prescribed depending on the outcome of national tenders

<sup>17</sup> Enforcement

<sup>18</sup> Typically only biosimilars can be dispensed if they win the contract

<sup>19</sup> Market share of biosimilar use in 2019 as a % of total biological utilization per molecule:

- Rituximab—37.3%
- Etanercept—35.2%
- Adalimumab—26%
| Country/ Region | Details of the initiatives | Influence/ outcome where known |
|-----------------|---------------------------|-------------------------------|
| France— various biosimilars *(Kim et al., 2020)* | • *Education*—Materials from the French authorities providing guidance on biosimilars  
• *Economics*—Additional remuneration for hospitals reaching biosimilar targets  
• *Engineering/ enforcement*—In 2017, ministerial instruction that 70% of naïve patients must be treated with a biosimilar when pertinent | • Utilization of infliximab biosimilar increased substantially in recent years reaching 48% by March 2018 and growing, with lower rates before this  
• It is envisaged that ongoing demand-side measures including those in hospitals in France will further accelerate uptake of biosimilars given NHS goals for 2022 *(Ministry of Health France, 2019)*  
• Variable usage in 2019 depending on the biosimilar (in DDDs/1000 inhabitants/day):  
  - *Infliximab*  
    - Originator—0.0  
    - Biosimilar—0.3  
  - *Etanercept*  
    - Originator—0.1  
    - Biosimilar—0.2  
  - *Adalimumab*  
    - Originator—0.3  
    - Biosimilar—0.2  
• In 2014, biosimilar infliximab was initially priced between 33% and 39% lower than the reference originator. As a result, winning the tender and enhancing the use of biosimilars  
• In 2015, the prices of biosimilars were further reduced to 51% to 69% lower than the reference product—making biosimilar infliximab the preferred bDMARD for all prescribed indications. This enhanced its market share to over 50% of total infliximab utilization  
• In 2016, biosimilar infliximab was still the cheapest alternative—60% lower than the originator price  
• In 2016, biosimilar etanercept was offered at 47% lower than the regular price of the originator again enhancing its use  
• In 2017—estimated savings were:  
  - *Infliximab*—GBP99.4 million  
  - *Etanercept*—GBP60.3 million  
  - *Rituximab*—GBP50.4 million  
• The uptake of biosimilars has increased with multiple activities:  
  - Biosimilar infliximab took 28 months to reach 80% penetration and after 12 months biosimilar etanercept reached 50% of eligible patients  
  - Biosimilar rituximab took 10 months to reach 80% of total rituximab and biosimilar trastuzumab only 8 months  
• In their study, Kim *et al.* (2020) found that infliximab biosimilar accounted for 89% of total infliximab by March 2018 through multiple activities *(Kim et al., 2020)*  
• Expenditure on adalimumab is envisaged to fall by 75% following the availability of biosimilars and aggressive contracting with multiple manufacturers *(Davio, 2018)* |
| Italy—various biosimilars *(Bertolani and Jommi, 2020)* | • *Education*—National and regional guidance on biosimilars and regional educational activities  
• *Dissemination*—Periodic publication of reports regarding current utilization and expenditure patterns  
• *Engineering*—Biosimilar prescribing targets including targets for new patients  
• *Economics*—Financial incentives for reaching agreed prescribing targets  
• *Enforcement*—Potential for and automatic substitution when pertinent |  |
| Norway—Infliximab and Etanercept *(Dörner *et al.*, 2016; IQVIA, 2020; Matusewicz *et al.*, 2015)* | • *Education*—The hospitals in Norway combine together with an annual bidding process with normally one winner covering a 12-month period  
• *Engineering and Economics*—This includes biosimilars for infliximab and etanercept when first available |  |
| United Kingdom (England)—various biosimilars *(NHS England, 2017; NHS England, 2019; NHS England, 2020; NHS England and NHS Improvement, 2019; Moorkens *et al.*, 2021)* | • *Education*—Variety of educational and other booklets discussing biosimilars were produced and disseminated  
• *Engineering*—A target of 90% was set for new patients to be prescribed the best-value biological medicine within 3 months of its launch as a biosimilar  
• Local health authorities actively encouraging switching to meet the goal of 80% biosimilar prescription rates within one year of launch where possible  
• Local health authority biosimilar adoption rates closely monitored and benchmarked through regional teams to enhance biosimilar uptake |  |

Continued
| Country/ Region | Details of the initiatives                                                                 | Influence/ outcome where known                                                                 |
|----------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| United Kingdom—Scotland—various biosimilars  
(Godman et al., 2020c; Health Improvement Scotland, 2018; Moorkens et al., 2021; NHS Scotland, 2018; NHS Scotland, 2019.) | Education, Engineering and Economics:  
• Multiple educational initiatives among all key stakeholder groups including publications addressing safety and effectiveness concerns with biosimilars  
• Prescribing targets for biosimilar use (new and existing patients)  
• Health Boards (Regions) regularly benchmarked against each other  
• Emphasizing pressure on budgets coupled with the continued desire to treat more patients with biological medicines |  
• Etanercept and infliximab biosimilars reached 84% and 94% of total utilization of these biologicals by December 2017  
• The prescribing of rituximab biosimilar had also risen to 74% of all rituximab by December 2017—its first year of availability  
• By December 2019, biosimilars for trastuzumab had accounted for 92% of all trastuzumab, and biosimilars for adalimumab 87% of all adalimumab and growing |

**Figure 1.** Utilisation of long-acting insulin analogues over time among selected European countries and Regions as a percentage of total insulins (DDD based)

**Figure 2.** Expenditure on long-acting insulin analogues over time as a percentage of total insulin expenditure among selected European countries and Regions
for the biosimilars for long-acting insulin analogues in particular, with the aim of benefiting all key stakeholder groups in the future.

**Biosimilar market (General)**

Among European countries, there have been considerable disparities in the prescribing of biosimilars in recent years (Table 2) as well as among Asian countries. These differences have been driven by concerns with their safety and effectiveness, limited price differences in practice between originators and biosimilars in a number of countries alongside limited instigation of demand-side measures to increase their prescribing (Godman et al., 2021a, 2021e; Kim et al., 2020; Moorkens et al., 2017; Tubic et al., 2021).

The instigation of multiple demand-side measures, along with greater price differentials, can appreciably enhance the uptake and use of biosimilars (Table 2). This mirrors the situation that has been seen with multiple-sourced oral medicines where the instigation of multiple demand-side measures has appreciably enhanced their preferential prescribing versus patented medicines.
A number of activities have potentially limited the attractiveness of 100 IU/ml strength insulin glargine for biosimilars in Albania. These include:

- Utilization (DDDs) of insulin glargine as a % of total long-acting analogues dropped by 51.4% from 2014 to early 2020 with expenditure falling by 47.2% during the same period although overall utilization of insulin glargine grew by 9.0% between 2014 and 2019

- In contrast, the utilization of Gla-300 grew from 3.4% of total insulin glargine dispensed in 2016 (DDDs) up to 56.3% in 2019, and is still growing

- The cost/DDD for insulin glargine 100 IU/ml was 32% lower between 2014 and early 2020 enhanced by price reductions by the originator company, with the cost/DDD Gla-300 also falling by 16.1% between 2016 and 2020

These factors may explain why biosimilar insulin glargine preparations have not currently been launched in Albania.

**Table 4. Potential rationale for the expenditure and utilization patterns seen for the different insulin glargine preparations seen among the studied European countries.**

| Country                        | Potential explanation for current utilization and expenditure patterns                                                                 |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Albania                        | A number of activities have potentially limited the attractiveness of 100 IU/ml strength insulin glargine for biosimilars in Albania. These include: |
|                                | - Utilization (DDDs) of insulin glargine as a % of total long-acting analogues dropped by 51.4% from 2014 to early 2020 with expenditure falling by 47.2% during the same period although overall utilization of insulin glargine grew by 9.0% between 2014 and 2019 |
|                                | - In contrast, the utilization of Gla-300 grew from 3.4% of total insulin glargine dispensed in 2016 (DDDs) up to 56.3% in 2019, and is still growing |
|                                | - The cost/DDD for insulin glargine 100 IU/ml was 32% lower between 2014 and early 2020 enhanced by price reductions by the originator company, with the cost/DDD Gla-300 also falling by 16.1% between 2016 and 2020 |

Bosnia and Herzegovina (B & H)  | Currently there is no automatic substitution for biosimilars in B & H. New government policies are needed in the different entities before such activities can take place, which need to be encouraged by clear guidance regarding their interchangeability and substitutability defined by the Agency for Medicinal Products and Medicinal Devices of B & H. Whilst the different State Agencies in B & H do encourage physicians to prescribe biosimilars rather than originators for new patients where this is possible, this does not always happen in practice exacerbated by the limited introduction of additional demand-side measures (Table 2) |
|                                | - Currently limited demand-side measures in B & H to date (Tubic et al., 2021) have resulted in: |
|                                |   - Utilization of Gla-300 rising from 4.2% of total insulin glargine in 2016 to 52.1% in 2019 enhanced by continued price reductions for Gla-300 (43%) helping maintain its appreciably lower cost/DDD versus 100 IU/ml formulation |
|                                |   - The company reducing its price originator 100 IU/ml over time thereby limiting price differences in practice between the originator and biosimilar (Table 3) further reducing the attractiveness of the biosimilar insulin glargine market |
|                                |   - Currently insufficient experience among physicians with switching from an originator biologic analogue to an appropriate biosimilar further reducing the attractiveness of the biosimilar |
|                                | - These combined activities have limited the utilization of biosimilar 100 IU/ml insulin glargine in practice in B & H |

Bulgaria                      | Whilst there has been growth in expenditure and utilization regarding long-acting insulin analogues in Bulgaria as a percentage of total insulin (Figs. 1 and 2) in recent years, the growth in the utilization of biosimilar insulin glargine as a percentage of total insulin glargine utilization has been more limited during the study period. Utilization of biosimilar insulin glargine rose from 9.3% of total insulin glargine in 2018 to 11% in 2020 |
|                                | - This limited increase could be explained by continuing marketing activities of the originator company, the lack of demand-side measures including physician incentives to preferentially prescribe biosimilars over originators and limited differences prices between the originator and the biosimilars in practice over time with both the originator and biosimilars reducing their prices with the lowest price/DDD reimbursed (Table 3) with the originator typically matching biosimilar prices (Tachkov et al., 2021) |

Estonia                      | There was limited utilization of 100 IU/ml biosimilars in Estonia during the study period despite appreciable utilization of long-acting insulin analogues. This could be explained by: |
|                                |   - The promotional activities of the originator company switched to patented Gla-300 alongside LANTUS SOLOSTAR pens to reduce competition, with utilization of Gla-300 growing from 4.7% of total insulin glargine in 2015 to 55.4% in 2020 |
|                                |   - The price of originator insulin glargine (100 IU/ml) dropped by 24.9% over time (Table 3). This resulted in limited price differences between the originator and biosimilars in practice in recent years (2.1%—7.1%) |
|                                |   - Currently limited demand-side measures in Estonia directing physician prescribing |

Hungary                      | Ongoing policies to enhance the use of biosimilar insulin glargine in Hungary include: |
|                                |   - A reference pricing system. This means that patients are required to fund themselves any difference in prices between the originator and any biosimilar |
|                                |   - Ongoing initiatives to encourage physicians to start new patients on a less expensive biosimilar |

However, the utilization of biosimilar insulin glargine 100 IU/ml has been moderated by:

- Increasing utilization of Gla-300 enhanced by promotional activities of the originator company with Gla-300 reaching 58.0% of total insulin glargine utilization by 2020

- The originator company lowering its price over time leading to just a 1.6% price difference in 2020 (Table 2)

Italy                      | In Italy, there have been ongoing policies to increase physicians prescribing of biosimilars. However, the limited prescribing of biosimilar insulin glargine 100 IU/ml has been influenced by: |
|                                |   - Growth in the prescribing of Gla-300 (48.8% in recent years) |
|                                |   - Appreciable price reduction of the originator over time (Table 3) |
| Country   | Potential explanation for current utilization and expenditure patterns |
|-----------|---------------------------------------------------------------------|
| Kosovo   | - The increased prescribing of long-acting insulin analogues in recent years in Kosovo reflects physician perceptions of their benefit to patients in terms of additional convenience and improved outcomes  
- However, there are concerns with the effectiveness and safety of biosimilar insulin glargine among physicians, which has resulted in no importation to date  
- Since 2015, biosimilars can only be registered and imported into Kosovo if they possess the necessary marketing authorization following a centralized procedure from the EMA or an approval from the FDA |
| Latvia    | No biosimilar insulin glargine 100 IU/ml has been launched to date in Latvia probably due to:  
- A 29.0% reduction in the utilization of glargine 100 IU/ml between 2014 and early 2020, with the prescribing of insulin glargine reducing by 7.9% as a percentage of overall insulin due to a growth in the utilization of other long-acting insulin analogues with ongoing promotional activities  
- Utilization of Gla-300 has grown from 27.7% of total insulin glargine in 2016 (DDD basis) to 51.4% in early 2020 through commercial and other activities  
- The originator company has decreased the price of insulin glargine 100 IU/ml by 14.4% in recent years (Table 3), and Gla-300 by 9.6%, further reducing the attractiveness of the biosimilar 100 IU/ml market |
| Lithuania | In Lithuania, there has been appreciably higher use of biosimilar insulin glargine compared with other Baltic Countries (Estonia and Latvia) in recent years—Figure 3. This may be due to:  
- Trends toward INN name prescribing in Lithuania coupled with the instigation of reference pricing which results in patients having to cover the additional costs themselves for a more expensive medicine  
- However, utilization of the 100 IU/ml formulation has been moderated by growing utilization of Gla-300 rising from 2.95% of total insulin glargine in 2015 to 39.03% in early 2020, enhanced by price reductions (13.7% between 2015 and 2020)  
- Similar reimbursed prices between 100 IU/ml originator and biosimilars—reflecting ongoing reference pricing in Lithuania with prices of medicines displayed in community pharmacies to enhance competition where there are co-payments |
| Poland    | The growth in the prescribing of long-acting insulin analogues in Poland in recent years, although from a lower base, may reflect a more cautious attitudes toward insulin long-acting insulin analogues generally coupled with issues of affordability  
- The appreciably higher utilization of biosimilar insulin glargine in recent years in Poland versus the originator compared with that seen among the other studied CEE countries (Fig. 3) may have been facilitated by a flat reimbursement rate. This means, similar to Lithuania, that patients must pay the price difference for a more expensive form of insulin glargine than the current reference priced product. In addition, the Ministry of Health in Poland is introducing measures to grow the prescribing of biosimilars in Poland to save resources, helped by Poland being a producer of biosimilars  
- However, the promotion of Gla-300 by the originator company has limited the prescribing of biosimilar 100 IU/ml with the utilization of Gla-300 reaching 37.1% of total insulin glargine by early 2020. This has been helped by prices of Gla-300 falling by 5.8% between 2017 and 2020 |
| Romania   | In recent years in Romania, the high expenditure on long-acting insulin analogues is a reflection of successful marketing by the originator companies. This is reflected by insulin glargine becoming one of the top selling medicines in recent years in Romania, and more recently the top selling medicine  
- In addition, in the fourth quarter of 2015, insulin detemir also became one of the top 10 medicines by value in Romania. Both helped to maintain high expenditures on long-acting insulin analogues in Romania in recent years  
- In Romania, an insulin glargine biosimilar has recently been reimbursed (Abasaglar® 100). However, to date there has been very limited uptake due to ongoing pricing and reimbursement policies alongside limited physician incentives or constraints (demand-side measures) to preferentially prescribing biosimilars coupled with no co-payment issues for patients  
- The current international reference pricing system in Romania may also discourage the launching biosimilars in Romania with fears of parallel exportation |
| Slovenia  | Whilst there is greater utilization of biosimilar insulin glargine in Slovenia in recent years as a percentage of total insulin glargine compared with other CEE countries, its prescribing has been affected by:  
- Overall in practice, there has been limited differences in prices between the originator and biosimilars with the originator company appreciably reducing its prices  
- Limited demand-side measures being instigated in practice by the health authority to encourage the preferential prescribing of biosimilars including biosimilar insulin glargine |

Continued
The utilization of biosimilar insulin glargine has been growing in Catalonia from 2.6% of total insulin glargine in 2015 to 12.4% in 2020 and 18.2% when considering just 100 IU/ml formulations. However, its usage has been limited due to a number of issues. These include:

- Growing usage of Gla-300, now accounting for 28.1% of total insulin glargine (DDD basis)
- Current pricing arrangements with no differences in reimbursed prices between the biosimilars and the originator (Table 3)
- Concerns among physicians with regular switching of patients between the originator and biosimilars

In addition, the situation seen with antimicrobials and compromise the future funding of medicines (with universal healthcare. This is because attempts to reduce to increase the prescribing of biosimilars, especially in countries, to enhance compliance

- Usage of long-acting insulin analogues including insulin glargine has been further affected by advice from NHS Scotland that patients should be started on human intermediate acting insulins, with long-acting insulin analogues only considered based on a patient’s hypoglycemic risk
- The Health Boards in Scotland (health authorities) regularly monitor the % of patients prescribed long-acting insulin analogues versus all long- and intermediate-acting insulins excluding bi-phasic insulins to enhance compliance
- These combined activities appear to have moderated the utilization of long-acting insulin analogues and biosimilars in Scotland in recent years versus a number of CEE countries (Fig. 1)
- Recommendations that long-acting insulins should be prescribed by brand name only to reduce the potential for hypoglycemia coupled with concerns with switching—although biosimilars should be considered for new patients, has further limited the prescribing of biosimilar insulin glargine in practice in Scotland
- The situation with biosimilar insulin glargine is different to that seen with biosimilars for infliximab, etanercept, trastuzumab, and rituximab where there was rapid uptake of these biosimilars in Scotland following the instigation of multiple demand-side measures—including quality indicators surrounding biosimilar use, e.g., by December 2019, biosimilars for trastuzumab had accounted for 92% of all trastuzumab and biosimilars for adalimumab 87% of all adalimumab and growing (Table 2)

Table 5 discusses potential measures that could be introduced among all key stakeholder groups across countries, broken down by the 4Es where pertinent (Table 1), to enhance the prescribing of biosimilars where issues and concerns still exist. This builds on the findings in Tables 2 and 4 alongside the considerable experience and expertise of the senior level co-authors. It is recognized by all key stakeholders that it is important to increase the prescribing of biosimilars, especially in countries with universal healthcare. This is because attempts to reduce their prescribing will make the biosimilar market unattractive and compromise the future funding of medicines (Godman et al., 2021a, 2021d). This will be detrimental to all key stakeholder groups in the coming years especially given the appreciable number of biologic medicines that are likely to soon lose their patents coupled with the need to fund new high priced medicines that address current unmet needs (Godman et al., 2021a, 2021e).

### Biosimilar long-acting insulin analogues

Insulin glargine is a different situation to the biosimilars of anti-TNF alphas, as well as adalimumab, rituximab, and trastuzumab in terms of increasing expenditure and use of long-acting insulin analogues among CEE countries (Figs. 1 and 2). This contrasts with previous low use of biological medicines to treat patients with immunological and oncological diseases in these countries (Baumgart et al., 2019; Godman et al., 2021a). This growing use reflects increasing recognition of the value and role of long-acting insulin analogues in managing patients with diabetes across countries although there can still be issues with affordability in some countries (Ewen et al., 2019; Godman et al., 2021d; Tricco et al., 2021).

There are though concerns with the low use of biosimilar insulin glargine in practice (Fig. 3) in a number of European countries versus the high use of biosimilars generally (Table 2).

The low use of biosimilar insulin glargine in a number of European countries (Fig. 3) may be due to a number of factors. These include the originator company lowering the price of 100 IU/ml insulin glargine and switching promotional efforts to Gla-300 (Tables 3 and 4). The situation with the manufacturer of originator insulin glargine promotion to the higher strength patented 300 IU/ml formulation is similar to previous evergreening activities by companies (Alkhafaji et al., 2012; Vernaz et al., 2013). Examples include switching promotion from omeprazole to esomeprazole and citalopram to escitalopram, increasing costs without necessarily improving patient care (Godman et al., 2018b, 2019b; Vernaz et al., 2013). Table 6 builds on Table 5 to review a number of activities that can be undertaken by key stakeholder groups across Europe to enhance future utilization of biosimilar insulin glargine 100 IU/ml. The instigation of such activities should encourage more companies and formulations of biosimilar long-acting insulin to launch new biosimilars. As a result, helping to lower prices, which should benefit all key stakeholders. It is also important for European...
Table 5. Potential strategies among all key stakeholder groups to enhance the prescribing of biosimilars across Europe where issues and concerns still exist.

| Stakeholder                  | Suggested activities                                                                                                                                 |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Education**                | • Undertake comprehensive educational programmes where concerns with biosimilars still exist among key stakeholder groups driven in part by originator companies. As part of this:  |
|                              |   • Actively disseminate the findings from landmark studies that demonstrate similar safety and effectiveness between a biosimilar and an originator, e.g., the Norwegian NOR-SWITCH study (Jorgensen et al., 2017)  |
|                              |   • Remind key stakeholders that originator companies have themselves sometimes quite frequently changed their manufacturing processes without currently needing to instigate additional studies demonstrating similar effectiveness and safety to the original compounds (Godman et al., 2020c; Jimenez-Pichardo et al., 2018; Vezer et al., 2016). This is despite becoming “biosimilars” themselves (Godman et al., 2020c, Godman, 2021)  |
|                              |   • Utilise key physician groups and societies to dispel existing misinformation regarding the safety and effectiveness of biosimilars versus originators that have been approved by regulatory agencies such as the EMA  |
|                              |   • Similarly use patient organizations and their representatives to:  |
|                              |     • Dispel misinformation regarding biosimilars  |
|                              |     • Broadcast the potential benefits of biosimilars in terms of reducing patient co-pays (where pertinent) as well as potentially enhancing funding for additional healthcare professions to treat more patients with cancer, diabetes and immunological diseases, where resources can be made available through increasing use of biosimilars  |
|                              |     • Communicate messages of similar effectiveness and safety between originators and biosimilars to reduce any nocebo affects that could negatively impact on biosimilar prescribing in routine clinical care (Coloca et al., 2019)  |
| **Engineering**              | • Instigate robust prescribing indicators to enhance the prescribing and dispensing of biosimilars arising from ongoing moves by originator companies to lower their prices in an attempt to dissuade biosimilar companies from entering the market/ continuing to compete—seen for both insulin glargine (Table 4) and recently with adalimumab in some countries (Moorckens et al., 2021)  |
|                              | • Re-look at taxes and rebates from originator companies if they appreciably reduce the price of their originator just prior to/ following biosimilar entry that reduces the differential between prices of the biosimilar and originator in practice and/ or reduces the attractiveness of the market for biosimilars in the first place (Table 4) (Moorckens et al., 2021). Alongside this, re-evaluate tendering process for off-patent biologicals and biosimilars building on current concerns and potential ways forward discussed by Barbier et al. (2021)  |
|                              | • Benchmark rates of biosimilar prescribing between physicians in a region/ nationally and regularly broadcasting the findings to enhance future prescribing of biosimilars  |
|                              | • Include prescribing of biosimilars as part of drug and therapeutic committee strategies in hospitals/ ambulatory care  |
|                              | • Ensure that any national treatment guidelines include preferential prescribing for biosimilars where pertinent, and ensure where possible there is no disagreement between entries in guidelines and reimbursement lists which can cause confusion (Kibuule et al., 2017)  |
| **Economics**               | • Financially incentivise physicians to preferentially prescribe biosimilars for both their existing and new patients  |
|                              | • Incentivise research into demonstrating similar effectiveness and safety of biosimilars versus originators as well as the extent of potential savings with increased use of biosimilars where such information is lacking. This also includes funding research into the cost-effectiveness of biosimilars where there are still concerns—building on existing studies (Dutta et al., 2020; Huang et al., 2020; Jang et al., 2021)  |
|                              | • Instigate greater co-payments for patients if they still wish originators when effective and safe biosimilars are available  |
|                              | • Consider value-added services from manufacturers of biosimilars to further enhance their value and utilization as part of procurement and other activities—especially if funding is needed to educate patients about any differences in devices between originators and biosimilars  |
|                              | • Instigate fines to pharmaceutical companies for any disinformation regarding biosimilars similar to the situation seen with the authorities in France regarding the level of disinformation with generic clopidogrel (Editorial, 2013)  |
| **Enforcement**             | • Potentially de-list or restrict the prescribing of higher priced originators from reimbursement lists/ lists of available medicines in hospitals where robust studies have demonstrated similar effectiveness and safety unless good reason—building on examples with angiotensin receptor blockers in Denmark (Hesse et al., 2013) as well as the current procurement systems for biological medicines in hospitals in Denmark and Norway (Jensen et al., 2020; Matuszewicz et al., 2015)  |
|                              | • Restrict the prescribing of more expensive patented biologicals that increase costs without improving care as seen with angiotensin receptor blockers in Austria and Croatia as well as duloxetine in Sweden (Godman et al., 2013; Voncina et al., 2011)  |
|                              | • Only reimburse/ procure biosimilars instead of originators once they become available to encourage greater competition among biosimilar manufacturers building on initiatives such as pre-qualification initiatives by the WHO for rituximab (WHO, 2020)  

Continued
health authorities to encourage companies to develop biosimilars for insulin glargine as this will help them justify investment to develop biosimilars for still patented long-acting insulin analogues. This will again benefit all key stakeholder groups across countries with growing prevalence rates for patients with diabetes. We will continue to monitor this.

**CONCLUSION**

Increased prescribing of low cost biosimilars is essential across Europe, as well as other countries seeking to attain or retain universal healthcare, given the continual resource pressures. These include pressures to fund new high-priced medicines to address unmet need despite at times limited health gain versus current standards. Increasing availability of biosimilars, and their use, will generate further confidence in their prescribing and lower costs without compromising care. However, a number of co-ordinated activities are needed to fully realize this.

There are also a number of issues with biosimilar insulin glargine which need to be overcome and addressed to enhance biosimilar use. These are in addition to potential activities to enhance biosimilar use generally. Key issues include addressing

| Stakeholder | Suggested activities |
|-------------|----------------------|
| Physicians and pharmacists (mainly education/engineering) | • Help with conducting future studies confirming no difference in effectiveness and safety between biosimilars (meeting standard quality requirements) and originators where there are continued concerns, and disseminating the findings in peer-reviewed journals. Similarly with any budget impact/cost-effectiveness analyses |
| | • Include the findings in future society guidelines and actively disseminate these in peer-reviewed journals and other media |
| | • Help with educating patients where pertinent regarding biosimilars and reducing any possible nocebo effect to limit any negative connotations associated with biosimilars (Colloca et al., 2019) |
| | • Help with the development of pertinent quality indicators and their measurement/dissemination as part of activities in the community/drug and therapeutic committees in hospitals to enhance biosimilar use |
| | • Work with health authorities to translate some of the savings from increased use of biosimilars into increased staffing levels where pertinent (particularly higher income European countries), as well as communicate with key stakeholder groups that more patients with immune diseases and cancer can be effectively treated with low-cost biosimilars to enhance their access/acceptability and use |
| | • Help with disseminating studies that demonstrate similar effectiveness and safety between originators and biosimilars to reduce current misinformation |
| | • Help with enlisting patients into pertinent studies where there is still uncertainty regarding the effectiveness and safety of biosimilars |
| | • Work with health authorities, physicians, pharmacists and others to translate potential savings from biosimilars into increasing staff levels/access to biological therapies especially where continuing concerns/sub-optimal staffing levels exist |

| Patient organizations | • Help with educating patients where necessary regarding similar safety and effectiveness between the originator and biosimilar insulin glargine. This includes actively broadcasting and disseminating the findings from ongoing real-world and other studies |
| | • Track any ongoing research regarding the potential savings/cost-effectiveness from biosimilar insulin glargine. Potential savings can subsequently be used to enhance the availability and prescribing of long-acting insulin analogues in potential patients where there are still concerns |
| | • Work with physicians and others to ensure patients are familiar with the different pens/devices where this exists between originators and biosimilars when there is switching between devices. As a result, minimize any potential for hypoglycemia |
| | • Alongside this, health authorities and others to work with patient organizations to facilitate greater use of biosimilar insulin glargine. This especially where there are resources/co-payment issues. Increased competition should help in lowering the prices of biosimilars benefitting all key stakeholder groups |
| | • Help with disseminating studies that demonstrate similar effectiveness and safety between originators and biosimilars to reduce current misinformation |
| | • Help with enlisting patients into pertinent studies where there is still uncertainty regarding the effectiveness and safety of biosimilars |
| | • Work with health authorities, physicians, pharmacists and others to translate potential savings from biosimilars into increasing staff levels/access to biological therapies especially where continuing concerns/sub-optimal staffing levels exist |

**Table 6.** Potential activities among European health authorities to enhance the prescribing and dispensing of insulin glargine biosimilars.
the evergreening activities of the originator company toward Gla-300 as well as addressing the limited price differences in practice between the biosimilars and the originator. Additional activities include enhancing physician and patient education where needed, increasing familiarity with the biosimilars as well as lowering prices, alongside multiple demand-side measures. Such coordinated measures should enhance the utilization of long-acting biosimilar analogues, which should benefit all key stakeholder groups going forward. This includes encouraging biosimilar manufacturers to develop biosimilars for other long-acting insulin analogues as they lose their patents.

AUTHOR CONTRIBUTIONS
All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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We did not seek ethical approval for this study as we were not dealing directly with patients. This is in agreement with national legislation and institutional guidelines.

DATA AVAILABILITY
All data generated and analyzed are included within this research article.

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