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REVIEW

Relevance of Adalimumab Product Attributes to Patient Experience in the Biosimilar Era: A Narrative Review

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ABSTRACT

Adalimumab (ADL, Humira®, reference product), an anti-TNF-α biologic, has transformed the treatment of chronic, immune-mediated inflammatory diseases. However, the high cost of ADL therapy has driven the development of more affordable ADL biosimilars, agents with no clinically meaningful differences from the reference product. This review summarizes the product attributes of reference ADL and the nine ADL biosimilars approved and available in the USA in relation to patient experience of injection-site pain (ISP). Product formulation, delivery volume and device features (e.g., type and needle gauge size) influence patient experience of ISP with potential clinical consequences. Citrate-free formulations generally cause less ISP; injection volumes of > 1.5 ml may be associated with increased ISP. Reference ADL and all ADL biosimilars offer a citrate-free formulation, and reference ADL and four ADL biosimilars offer a high-concentration solution that allows a smaller injection volume. All available ADL products are injected subcutaneously using either a pre-filled pen (PFP) or pre-filled syringe (PFS). Patients prefer the PFP, but the PFS permits better control over the speed and duration of injection. Smaller (29-gauge) needle outer diameter is associated with less ISP; reference ADL and seven ADL biosimilars offer a device with a 29-gauge needle. In the USA, an approved biosimilar can be designated "interchangeable," allowing pharmacy-level substitution, where state law permits. In the USA, two ADL biosimilars have received interchangeability designation; others are seeking interchangeability designation from the Food and Drug Administration ($n = 2$), are being evaluated in clinical studies to support interchangeability ($n = 2$), or do not have/are not

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seeking interchangeability designation (n = 3). Product-related attributes influence patient experience of ISP caused by subcutaneous ADL injection. Reference ADL and ADL biosimilar products differ in their attributes, so discussion with patients about treatment options is essential to optimize adherence and outcomes.

Keywords: Adalimumab; Biosimilar; Formulation; Interchangeability

Key Summary Points

Adalimumab (ADL), an anti-TNF-α biologic, is administered by subcutaneous injection using a pre-filled syringe or pre-filled pen.

Subcutaneous administration of biologic drugs, such as ADL, can be associated with injection-site pain (ISP), and patient experience of ISP is influenced by various product-related factors (e.g., formulation, delivery device and needle gauge size, and injection volume).

Biosimilar versions of reference ADL (Humira®) are approved and available on the US market; these agents are highly similar to and have no clinically meaningful differences in safety, purity, or potency from reference ADL.

ADL products (reference and biosimilar) differ in their attributes, and this can impact the injection experience and, by extension, treatment adherence and patient outcomes.

It is important for healthcare professionals to consider the various features of ADL products (reference and biosimilar) as well as the impact of interchangeable biosimilars and availability of patient assistance programs on patient access to these medications when discussing ADL treatment options with their patients.

DIGITAL FEATURES

This article is published with digital features, including a plain language summary as supplementary material, to facilitate understanding of the article. To view digital feature for this article, go to https://doi.org/10.6084/m9.figshare.2516446

INTRODUCTION

Adalimumab (ADL) is a recombinant, fully human IgG1 monoclonal antibody against tumor necrosis factor alpha (TNF-α) that reduces symptoms and improves physical function in patients with chronic immune-mediated inflammatory diseases [1]. ADL has been marketed as Humira® ([adalimumab], AbbVie Inc, North Chicago, IL, USA; AbbVie Deutschland GmbH Co. KG, Ludwigshafen, Germany) in the USA since 2002 [2].

ADL is used in the clinical practice of dermatologic, rheumatologic, and gastroenterologic diseases [3–11], and biosimilar versions of ADL are also available. A biosimilar is a biologic product that is highly similar to and has no clinically meaningful differences in safety, purity, or potency from the licensed reference or originator product [12]. The development and regulatory approval of a biosimilar is different from the process used for a reference biologic product or small-molecule drug and so is described with unique terminology (Table 1) [12–18]. The Biologics Price Competition and Innovation (BPCI) Act of 2009 created an abbreviated development pathway for biosimilars in the USA [19]. The BPCI Act established a framework to foster innovation and promote competition through the development of biosimilar products that have the potential to reduce treatment costs and expand access to safe and effective biologic therapies [19, 20].

Biologic drugs, such as ADL, cannot be administered orally; they can be administered by intravenous infusion or, most commonly, subcutaneous (SC) injection using a pre-filled syringe (PFS) or pre-filled pen (PFP). SC administration of biologic drugs can be associated with a subjective level of local pain and

Table 1 Key terms used to describe biosimilars

Term	Definition
Biologic drug [13–15]	Large, high-molecular-weight products with complex structures that are isolated from a natural source (e.g., humans, animals, and microorganisms) and produced using biotechnology and other cutting-edge technologies
	Biologic drugs include products such as, vaccines, blood and blood components, allergenics, cells and tissues, and recombinant therapeutic proteins
Biosimilar [12, 14]	A biologic product that is highly similar to and has no clinically meaningful differences in safety, purity and potency from the licensed reference or originator product
Conventional drug [14]	Small, low-molecular-weight compounds with simple structures that are produced through chemical synthesis
Generic drug [18]	A medication created to be identical to the brand-name conventional drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use
Interchangeable biosimilar [16, 17]	In the USA, a biosimilar may achieve an additional regulatory designation for interchangeability
	An interchangeable biosimilar "can be expected to produce the same clinical result as the reference product in any given patient" and demonstrates "for products that are administered more than once the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch"
	Interchangeable biosimilars may be substituted for the reference product without the intervention of the HCP who prescribed the reference product, where state law permits
Reference or originator product [12]	An already approved biologic product against which a proposed biosimilar product is compared

HCP Healthcare provider

irritation [21]. Many product-related factors may influence the extent of injection-site pain (ISP) during SC injection, including formulation, delivery volume, and needle gauge size [21, 22]. In addition, patients may prefer one device type (PFS or PFP) because of aspects such as convenience and ease of use, perception of pain, or fear of injection [21, 23–32].

Many ADL products (reference and biosimilar) are available that differ in their formulations and delivery device features, which can impact the injection experience. Here, we review the attributes of reference ADL and the ADL biosimilars approved and available in the USA that may help to better inform patient choice of treatment.

METHODS

Relevant peer-reviewed literature on the topics of SC injection with ADL and ADL biosimilars were identified based on the experience of the authors. Furthermore, regulatory documents (e.g., Food and Drug Administration [FDA] submissions/reviews) and product labels (e.g., US prescribing information) were searched for details of product attributes for ADL products.

This article is based on previously conducted studies and other sources; it does not contain any studies with human participants or animals performed by any of the authors.

ADL Biosimilars in the USA

As of October 2023, nine ADL biosimilars have been approved and are available on the market in the USA (Table 2) [33–43]. Additionally, a biologics license application for one proposed ADL biosimilar (AVT02, Alvotech, Reykjavik, Iceland) was accepted by the US FDA with anticipated approval in February 2024 [44].

Relevance of ADL Product Attributes to the Injection Experience

Formulation

Controlling pH is necessary for the solubility and stability of SC-injected biologic drugs. Slightly acidic formulations may be preferred for drug stability, but formulations with pH < 3.0 can cause pain and inflammation [21, 22]. Basic formulations with pH > 9.0 are associated with tissue necrosis [21, 22]. pH is often controlled by adding buffer salts to a product formulation [53].

Citrate and phosphate are two of the most used buffers and have a wide buffering range (pH 2.1–6.2 and 3.0–8.0, respectively) [22, 54]. Newer monoclonal antibody formulations use histidine or acetate as the preferred buffer; however, the buffering range (pH 5.0–6.5 and 3.8–5.8, respectively) is narrower versus phosphate or citrate [22, 55]. Citrate has been used in > 100 injectable product formulations [54]. However, stabilizing pH with citrate buffers has been associated with ISP [56, 57]. In addition, glutamate has been used as an excipient for product stability, and SC injection of glutamate has been associated with ISP and injection-site reactions [21, 58].

In a prospective single-center study of 54 adult healthy volunteers, a significantly greater number of participants (38/54; 70%) injected with a citrate-containing solution reported more or much more pain immediately after injection than participants injected with a histidine-containing solution ($p = 0.002$) [56]. In a prospective observational registry study in patients with inflammatory bowel disease, switching from a citrate-free reference ADL to a citrate-containing ADL biosimilar was correlated with ISP ($p = 0.004$) [57].

The consequences of ISP can be clinically meaningful and may contribute to non-adherence and the patient's decision to discontinue treatment [59–61]. For example, in an online survey of patients with rheumatoid arthritis (RA; $n = 250$), the injection experience, including pain, burning, or discomfort during or after administration, was reported among the primary reasons for discontinuing a TNF inhibitor (TNFi) [59]. In a real-world study of rheumatology, dermatology, and gastroenterology patients receiving ADL ($n = 744$), the switch failure rate was higher for patients switched from citrate-free reference ADL to a citrate-containing ADL biosimilar than for patients switched to a citrate-free ADL biosimilar [61].

Formulating reference ADL to minimize ISP has been demonstrated to reduce the sensation of pain on administration [62, 63]. For example, in a pooled analysis of two identical, Phase 2, randomized, crossover studies in patients with RA, patients given citrate-free reference ADL reported less pain immediately after injection ($p < 0.001$) and were more likely to rate ISP severity as mild compared with patients given citrate-containing reference ADL (86.9% vs 42.6%) [62]. Citrate-free reference ADL was found to reduce ISP and was associated with greater treatment adherence, higher treatment persistence, and better experience of self-administration [64, 65].

Product formulations of ADL biosimilars available in the USA are summarized in Table 3 [2, 33–41]. High-concentration reference ADL and nearly all the ADL biosimilars offer versions that are citrate-, phosphate-, and glutamate-free [2, 33–41]. This is an important consideration when discussing ADL treatment options as patients and hospitals may not want to use products containing excipients that contribute to ISP.

Table 2 ADL biosimilars approved by the US FDA

Product	Brand name (INN)	Company	Regulatory approval date	Interchangeability designation?
ABP-501 [34]	Amjevita™ (adalimumab-atto)	Amgen Inc., Thousand Oaks, CA	2016	Multi-switch study completed [45]
AVT02 [44]	–	Alvotech, Reykjavik, Iceland	Anticipated approval February 2024	Application for interchangeability accepted by FDA [44]
BI 695501 [35]	Cyltezo® (adalimumab-adbm)	Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA	2017	Yes [46]
CHS-1420 [41]	Yusimry™ (adalimumab-aqvh)	Coherus BioSciences, Inc., Redwood City, California, USA	2021	Interchangeability designation will not be pursued [47]
CT-P17 [40]	Yuflyma® (adalimumab-aaty)	Celltrion, Inc., Incheon, Republic of Korea	2023	Application for interchangeability filed with FDA [48]
FKB327 [37]	Hulio® (adalimumab-fkjp)	Mylan Pharmaceuticals, Inc., Morgantown, WV, USA/Fujifilm Kyowa Kirin Biologics Co., Ltd/Biocon Biologics, Ltd., Bengaluru, Karnataka, India	2020	Multi-switch study completed [49]
GP2017 [38]	Hyrimoz® (adalimumab-adaz)	Sandoz Inc., Princeton, NJ, USA	2018	No [46]
MSB11022 [39]	Idacio® (adalimumab-aacf)	Fresenius Kabi USA, LLC, Lake Zurich, IL, USA	2022	Interchangeability designation will not be pursued [50]
PF-06410293 [33]	Abrilada™ (adalimumab-afzb)	Pfizer Inc., New York, NY, USA	2019	Yes [46, 51]
SB5 [36]	Hadlima™ (adalimumab-bwwd)	Samsung Bioepis Co., Ltd., Incheon, Republic of Korea/Organon & Co., Jersey City, NJ, USA	2019	Application for interchangeability filed with FDA [52]

ADL Adalimumab; *FDA* Food and Drug Administration; *INN* international non-proprietary name

Table 3 Key product-related factors for reference ADL and ADL biosimilars available in the USA

Brand name (INN)	Reference ADL	ADL biosimilar								
	Humira® [adalimumab] [2, 66]	**Abrilada™** [adalimumab-afzb] [33, 67]	**Amjevita™** [adalimumab-atto] [34, 68]	**Cyltezo®** [adalimumab-adbm][a] [35, 69, 70]	**Hadlima™** [adalimumab-bwwd] [36, 71]	**Hulio®** [adalimumab-fkjp] [37]	**Hyrimoz®** [adalimumab-adaz] [38]	**Idacio®** [adalimumab-aacf] [39]	**Yuflyma®** [adalimumab-aaty] [40, 72]	**Yusimry™** [adalimumab-aqvh] [41, 73, 74]
Formulation										
Ph	5.2	5.5	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.3
Standard concentration									N/A	
Citrate-free		✔	✔	✔		✔		✔		✔
Phosphate-free		✔	✔	✔	✔	✔	✔	✔		✔
Glutamate-free	✔	✔	✔	✔	✔		✔	✔		✔
Histidine-containing		✔			✔					✔
Acetate-containing			✔	✔				✔		
High concentration		N/A		N/A[a]		N/A		N/A		N/A[a]
Citrate-free	✔		✔		✔		✔		✔	
Phosphate-free	✔		✔				✔		✔	
Glutamate-free	✔		✔		✔		✔		✔	
Histidine-containing					✔					
Acetate-containing									✔	

Table 3 continued

Brand name (INN)	Reference ADL	ADL biosimilar								
	Humira® [adalimumab] [2, 66]	Abrilada™ [adalimumab-afzb] [33, 67]	Amjevita™ [adalimumab-atto] [34, 68]	Cyltezo® [adalimumab-adbm][a] [35, 69, 70]	Hadlima™ [adalimumab-bwwd] [36, 71]	Hulio® [adalimumab-fkjp] [37]	Hyrimoz® [adalimumab-adaz] [38]	Idacio® [adalimumab-aacf] [39]	Yuflyma® [adalimumab-aaty] [40, 72]	Yusimry™ [adalimumab-aqvh] [41, 73, 74]
Device type and needle size										
PFS	29-G and 27-G[b]	29-G	29-G	27-G[c]	29-G	29-G	29-G	29-G	29-G	27-G
PFP	29-G and 27-G[b]	29-G	27-G[c]	27-G	29-G	29-G	29-G	29-G	29-G	29-G
Dosing and delivery volume										
Standard concentration										
10 mg/0.2 ml	✔	✔	✔	✔			✔			
20 mg/0.4 ml	✔	✔	✔	✔		✔	✔			
40 mg/0.8 ml	✔	✔	✔	✔	✔	✔	✔	✔		✔
High concentration										
10 mg/0.1 ml	✔						✔			
20 mg/0.2 ml	✔		✔				✔		✔	
40 mg/0.4 ml	✔		✔		✔		✔		✔	
80 mg/0.8 ml	✔		✔				✔		✔	

Table 3 continued

Brand name (INN)	Reference ADL	ADL biosimilar								
	Humira® [adalimumab] [2, 66]	Abrilada™ [adalimumab-afzb] [33, 67]	Amjevita™ [adalimumab-atto] [34, 68]	Cyltezo® [adalimumab-adbm][a] [35, 69, 70]	Hadlima™ [adalimumab-bwwd] [36, 71]	Hulio® [adalimumab-fkjp] [37]	Hyrimoz® [adalimumab-adaz] [38]	Idacio® [adalimumab-aacf] [39]	Yuflyma® [adalimumab-aaty] [40, 72]	Yusimry™ [adalimumab-aqvh] [41, 73, 74]
Storage conditions										
Regular storage conditions (2°–8°C [36°–46°F])	Protected from light until ready for use, up to expiration date									
Approved alternative storage conditions	Protected from light until ready for use									
25°C (77°F)	14 days		14 days	14 days	14 days	14 days	14 or 21 days[d]	28 days	31 days	14 days
30°C (86°F)		30 days								

ADL adalimumab; *INN* international non-proprietary name; *N/A* not applicable; *PFP* pre-filled pen; *PFS* pre-filled syringe; *USPI* US prescribing information

[a]High-concentration formulation in development [75, 76]

[b]29-G and 27-G needles are available for high- and standard-concentration formulations, respectively, based on a USPI from 2017 [66]

[c]Based on the USPI from initial approval and for the 40 mg/0.8 ml concentration only [68, 70]

[d]Twenty-one days for the standard-concentration formulation and 14 days for the high-concentration formulation

Delivery Volume

Large SC injection volumes are generally associated with pain and adverse events at the injection site. In addition, the association between injection volume and ISP may be influenced by injection site location as injections into the thigh have been reported to be more painful than those into the abdomen [22, 77, 78]. Volumes of up to 0.8 ml are not expected to increase pain [22, 77, 78], but volumes of > 1.5 ml may be associated with increased ISP [21, 22, 79]. This observation is consistent with anecdotal reports from physicians and nurses that patients receiving 80 mg/0.8 ml loading doses of citrate-free ADL have not reported greater levels of ISP compared with those who received 40 mg/0.4 ml doses, though no formal assessments were conducted.

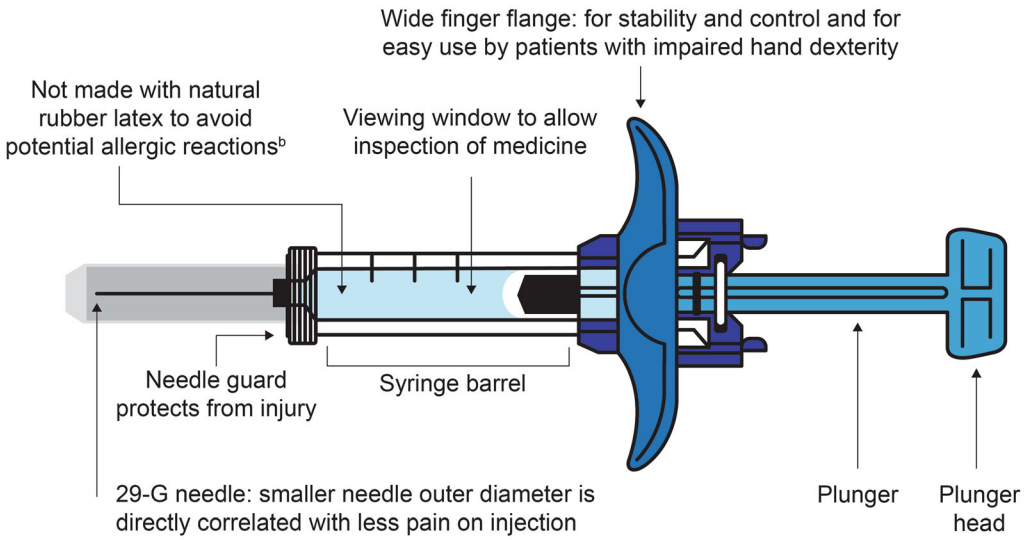
Reference ADL is available in a standard- (50 mg/ml) and high-concentration (100 mg/ml) solution for PFS or PFP injection [2]. Among currently available ADL biosimilars in the USA (Table 3), eight offer a standard-concentration solution (50 mg/ml) for injection by PFS or PFP [33–39, 41], and four offer a high-concentration solution (100 mg/ml) that allows a smaller volume for PFS or PFP injection: Amjevita™ (adalimumab-atto; Amgen Inc., Thousand Oaks, CA, USA), Hadlima™ (adalimumab-bwwd; Samsung Bioepis Co., Ltd., Incheon, Republic of Korea/Organon & Co., Jersey City, NJ, USA), Hyrimoz® (adalimumab-adaz; Sandoz Inc., Princeton, NJ, USA), and Yuflyma® (adalimumab-aaty; Celltrion, Inc., Incheon, Republic of Korea) [34, 36, 38, 40].

Device: Type, Needle Gauge Size, and Other Features

Reference ADL and all ADL biosimilars in the USA are available for injection as a PFS or PFP (Table 3) [2, 33–41]. Key features of ADL products available as a PFS or PFP are summarized in Figs. 1 and 2, respectively [2, 33–41, 66–74, 80–86]. The ADL PFS is composed of a needle and a syringe that is pre-filled with the appropriate drug dose, which reduces the time taken for injection and the chance of a dosing error and reduces the possibility of microbiologic contamination [87]. ADL PFPs have been designed so that the injection process is automated; their features make the injection process easier, which increases patient confidence [87, 88].

It is also important to consider both the inner and outer diameters of needles to fully understand the potential impact of varying needle gauges (Fig. 3). Smaller needle outer diameter is directly correlated with less pain on injection [89]. This may be an important factor to consider when discussing ADL treatment options as some patients may be able to differentiate between standard 27-gauge and smaller 29-gauge needle sizes [90]. In addition, it is important to consider whether natural rubber latex or synthetic derivatives of natural rubber latex were used as materials in the manufacture of the ADL product or its container to avoid potential allergic reactions [91]. Reference ADL offers a PFS and PFP with a smaller, 29-gauge needle size, and the needle cover of high-concentration PFS and PFP presentations of reference ADL is not made with natural rubber latex [2, 66]. Among currently available ADL biosimilars in the USA, seven offer a PFS or PFP with a smaller 29-gauge needle size (Table 3; Figs. 1 and 2) [34, 37–39, 67, 71–73], and eight are not made with natural rubber latex (Figs. 1 and 2) [33, 34, 38, 39, 41, 71, 72, 85]. Specifically, labeling for three ADL biosimilars (Hulio® [adalimumab-fkjp], Idacio® [adalimumab-aacf], and Yusimry™ [adalimumab-aqvh]) indicates a particular part of the presentation (plunger stopper, needle cover/cap, or both) is not made with natural rubber latex [39, 41, 85], and labeling for four ADL biosimilars (Amjevita [adalimumab-atto], Hadlima [adalimumab-bwwd], Hyrimoz [adalimumab-adaz], and Yuflyma [adalimumab-aaty]) does not specify a particular part of the presentation as not made with natural rubber latex meaning that it applies to the entire device [34, 38, 71, 72]. In addition, updated labeling for one ADL biosimilar (Abrilada™ [adalimumab-afzb], Pfizer Inc., New York, NY, USA) has received regulatory approval to include the statement "not made with natural rubber latex" as it applies to the entire device; this updated labeling is expected in April 2024 [33].

Currently available PFPs (Fig. 2) offer various features that support the safe and correct self-

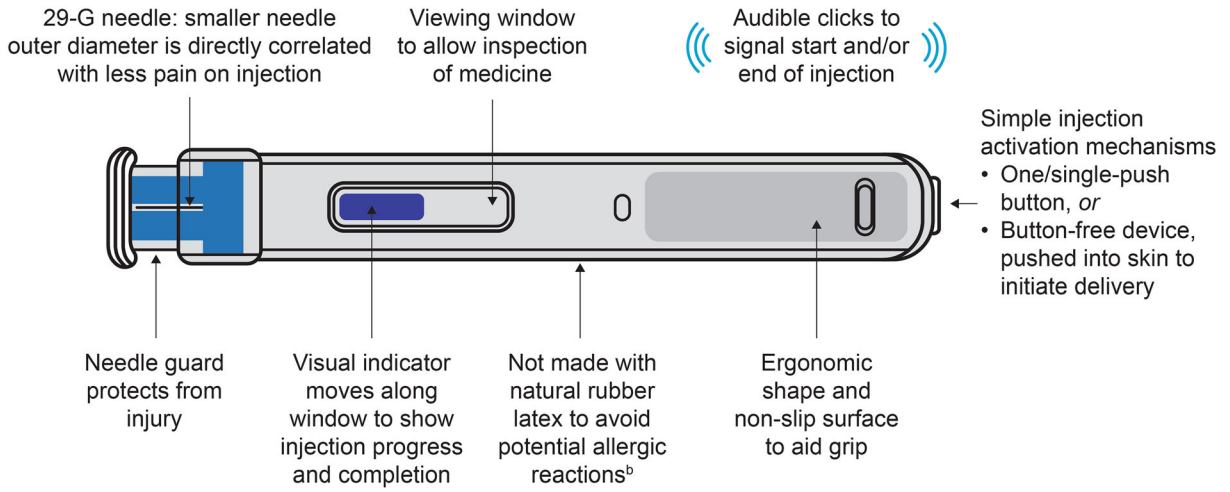


Product, brand name (INN)	Single use (expiration date on syringe)	Not made with natural rubber latex[b]	29-G needle	Wide finger flange	Viewing window	Needle safety guard	Rate of injection controlled by patient
Humira® [adalimumab] [2, 66]	✓	◆◆	✓	✓	✓		✓
Abrilada™ [adalimumab-afzb] [33, 67]	✓	■	✓	✓	✓		✓
Amjevita™ [adalimumab-atto] [34, 68]	✓	■	✓	✓	✓		✓
Cyltezo® [adalimumab-adbm] [35, 69, 70]	✓	☒		✓	✓		✓
Hadlima™ [adalimumab-bwwd] [36, 71, 80]	✓	■	✓	✓	✓	✓	✓
Hulio® [adalimumab-fkip] [37, 85, 86]	✓	◆	✓	✓	✓	✓	✓
Hyrimoz® [adalimumab-adaz] [38]	✓	■	✓	✓	✓	✓	✓
Idacio® [adalimumab-aacf] [39, 81]	✓	◆	✓	✓	✓	✓	✓
Yuflyma® [adalimumab-aaty] [40, 72]	✓	■	✓	✓	✓	✓	✓
Yusimry™ [adalimumab-aqvh] [41, 83, 74]	✓	◆		✓	✓		✓

☒ Needle cap contains natural rubber latex ■ Entire device not made with natural rubber latex ◆ Syringe plunger stopper, needle cap/cover, or both, not made with natural rubber latex
◆◆ Needle cover of standard-concentration presentations may contain natural rubber latex; Needle cover of high-concentration presentations is not made with natural rubber latex

Fig. 1 PFS features of reference ADL and ADL biosimilars approved and available on the US market.[a] [a]This is a generic depiction of the device based on features of available PFSs. [b]Labeling for Humira® (adalimumab) indicates the needle cover of standard-concentration presentations may contain natural rubber latex, while the needle cover of high-concentration presentations is not made with natural rubber latex [2]. Labeling for Hulio® (adalimumab-fkjp), Idacio® (adalimumab-aacf), and Yusimry™ (adalimumab-aqvh) indicates a particular part of the presentation (plunger stopper, needle cover/cap, or both) is not made with natural rubber latex [39, 41, 85]. Labeling for Amjevita™ (adalimumab-atto), Hadlima™ (adalimumab-bwwd), Hyrimoz® (adalimumab-adaz), and Yuflyma® (adalimumab-aaty) includes the statement "not made with natural rubber latex" as it applies to the entire device [34, 38, 71, 72]. In addition, updated labeling for Abrilada™ (adalimumab-afzb) has received regulatory approval to include the statement "not made with natural rubber latex" as it applies to the entire device; this updated labeling is expected in April 2024 [33]. ADL, adalimumab; G, gauge; INN, international non-proprietary name; PFS, pre-filled syringe

administration of ADL, including smaller needle outer diameter for less painful injections, a viewing window to inspect medication and ensure it is not cloudy or contaminated, a visual indicator that moves along the window to show injection progress, simple injection activation mechanisms to initiate drug delivery, audible clicks to signal the start and end of injection,



Product, brand name (INN)	29-G needle	Viewing window	Audible click	Simple injection activation mechanisms	Needle guard	Not made with natural rubber latex[b]	Visual indicator
Humira® [adalimumab] [2, 66]	✓	✓	✓	✓	✓	◆ ◆	✓
Abrilada™ [adalimumab-afzb] [33, 67]	✓	✓	✓	✓	✓	☑	✓
Amjevita™ [adalimumab-atto] [34, 68]		✓	✓	✓	✓	☑	✓
Cyltezo® [adalimumab-adbm] [35, 69]		✓	✓	✓	✓	☒	✓
Hadlima™ [adalimumab-bwwd] [36, 71, 80]	✓	✓	✓	✓	✓	☑	✓
Hulio® [adalimumab-fkip] [37, 82, 85]	✓	✓	✓	✓	✓	◆	✓
Hyrimoz® [adalimumab-adaz] [38]	✓	✓	✓	✓	✓	☑	✓
Idacio® [adalimumab-aacf] [39]	✓	✓	✓	✓	✓	◆	✓
Yuflyma® [adalimumab-aaty] [40, 72]	✓	✓	✓	✓	✓	☑	✓
Yusimry™ [adalimumab-aqvh] [41, 73, 84]	✓	✓	✓	✓	✓	◆	✓

☒ Needle cap contains natural rubber latex ☑ Entire device not made with natural rubber latex ◆ Syringe plunger stopper, needle cap/cover, or both, not made with natural rubber latex
◆ ◆ Needle cover of standard-concentration presentations may contain natural rubber latex; Needle cover of high-concentration presentations is not made with natural rubber latex

Fig. 2 PFP features of reference ADL and ADL biosimilars approved and available on the US market.[a] [a]This is a generic depiction of the device based on features of available PFPs. [b]Labeling for Humira® (adalimumab) indicates the needle cover of standard-concentration presentations may contain natural rubber latex, while the needle cover of high-concentration presentations is not made with natural rubber latex [2]. Labeling for Hulio® (adalimumab-fkjp), Idacio® (adalimumab-aacf), and Yusimry™ (adalimumab-aqvh) indicates a particular part of the presentation (plunger stopper, needle cover/cap, or both) is not made with natural rubber latex [39, 41, 85]. Labeling for Amjevita™ (adalimumab-atto), Hadlima™ (adalimumab-bwwd), Hyrimoz® (adalimumab-adaz), and Yuflyma® (adalimumab-aaty) includes the statement "not made with natural rubber latex" as it applies to the entire device [34, 38, 71, 72]. In addition, updated labeling for Abrilada™ (adalimumab-afzb) has received regulatory approval to include the statement "not made with natural rubber latex" as it applies to the entire device; this updated labeling is expected in April 2024 [33]. ADL, adalimumab; G, gauge; INN, international non-proprietary name; PFP, pre-filled pen

and a needle guard to minimize needle phobia and protect from injury [2, 33–41, 66–68, 71–73, 80, 82, 84]. In addition, reference ADL and four ADL biosimilars offer single-dose pens that are currently licensed for the Arthritis Foundation's Ease of Use Certification [69, 92, 93]. Products receiving the Arthritis Foundation's Ease of Use Certification have been independently tested and proven as easier to use for people living with arthritis, chronic pain and limited functionality [92]. These device attributes should be considered when discussing ADL treatment options as patients switching from reference ADL to an ADL

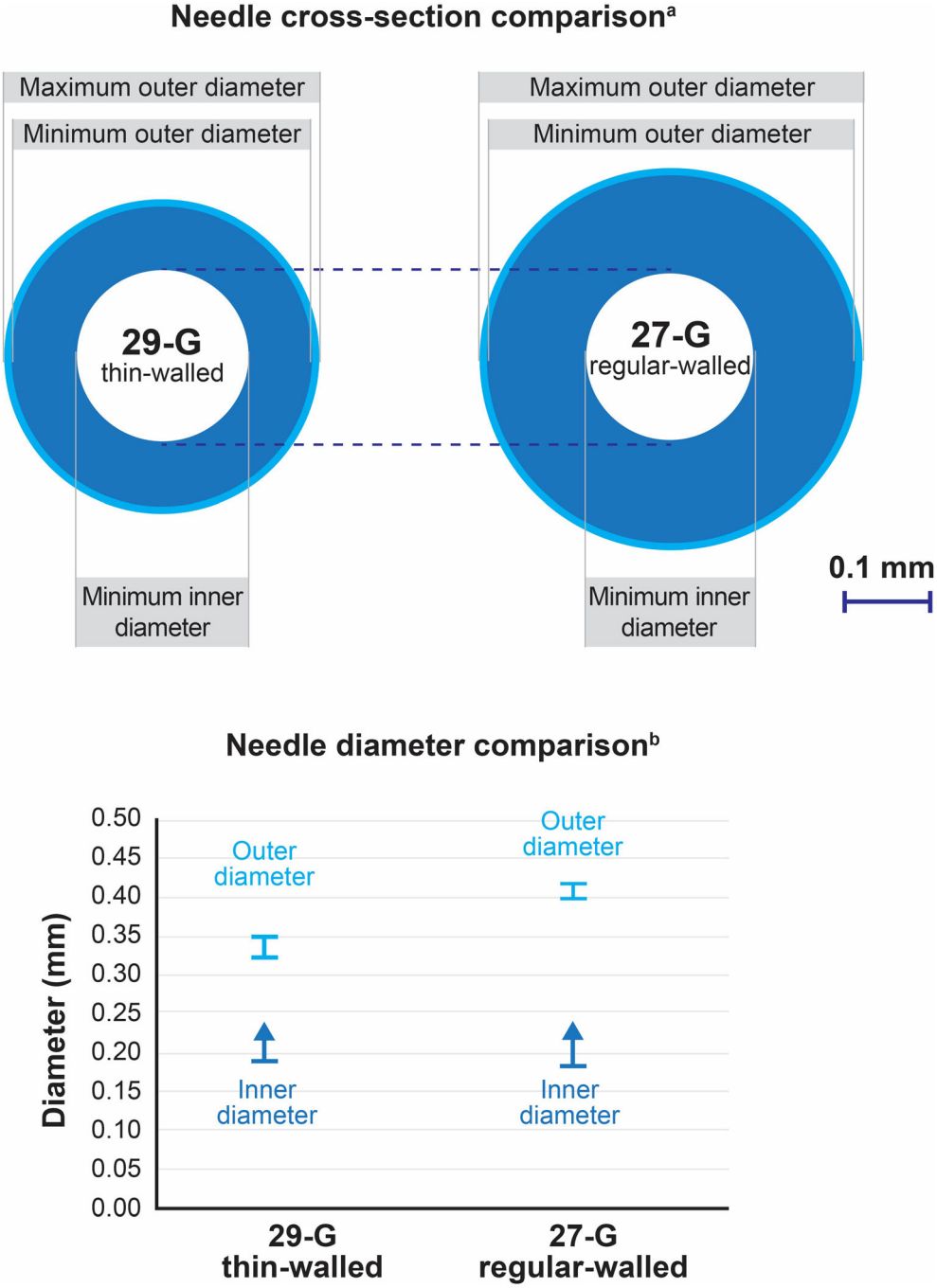


Fig. 3 Comparison of 29-G thin-walled and 27-G regular-walled needle diameters. [a]The 29-G thin-walled and 27-G regular-walled needles have different outer diameters, but a comparable inner diameter. Therefore, patients can apply the same force to the injection device to administer medicine at the same speed because it passes through the same size area. [b]The 29-G thin-walled needle measurements are based on the needle used in Abrilada™ (adalimumab-afzb). The outer diameter measurements relate to all 29-G and 27-G needles; however, the inner diameter measurement may not be representative of needles used with other ADL products. *ADL* adalimumab; *G* gauge

biosimilar may find it easier to transition to a PFP that is similar to the reference ADL PFP.

In general, most patients prefer a PFP over a PFS because they are convenient, quick, comfortable, and easy to use and because they have built-in safety features [24, 28, 30, 32]. However, some patients who experience ISP, which may be influenced by pain catastrophizing and can cause dread of injecting over time [21, 29], may prefer to use a PFS because the device allows better control over the speed and duration of injection as compared with a PFP [31, 94].

A preference for PFP devices has been demonstrated in patients administering reference ADL. In a Phase 2 trial (TOUCH study) of reference ADL in patients ($N = 52$) with RA, 88.5% preferred using a PFP compared with 5.8% who preferred using a PFS to administer reference ADL, citing less pain (76.9%), ease of use (94.2%), and convenience (92.3%) as advantages [28]. In a Phase 3 trial of the ADL biosimilar PF-06410293 (Abrilada [adalimumab-afzb]] in patients ($N = 50$) with RA, nearly all patients (95.9% [47/49]) elected to continue study treatment using PFP injections after completing the device usability sub-study [25]. In a Phase 2, open-label study of the ADL biosimilar SB5 (Imraldi® [adalimumab], Samsung Bioepis Co., Ltd., Incheon, Republic of Korea/Hadlima [adalimumab-bwwd]) in 49 patients with RA, 30.4% and 56.5% of patients ($N = 46$) reported an overall preference for the PFS and PFP, respectively, at week 6 [26].

Self-injection of a TNFi can improve the patient treatment experience, and availability of choice in self-injection device can address psychologic (e.g., injection anxiety, needle phobia) and physical (e.g., impaired hand dexterity, hand pain) barriers to safe self-injection leading to improved treatment adherence and patient outcomes [87, 88].

Out of Fridge Stability

Under normal circumstances, ADL must be refrigerated (2 °–8 °C [36 °–46 °F]); however, if needed (e.g., when traveling), ADL may be stored under alternative conditions (Table 3) [2, 33–41]. All ADL products can be stored at 25 °C (77 °F) with storage durations ranging from 14 to 31 days (Table 3), as determined from stability studies and specified in the product labelling instructions [2, 33–41, 95, 96]. One ADL biosimilar, Abrilada (adalimumab-afzb), may be stored at temperatures of up to 30 °C (86 °F) for 30 days [33]. Extended stability of ADL at room temperature conditions offers convenience and flexibility in storage, which could improve the injection experience and may lead to better treatment adherence and patient outcomes.

ADL Biosimilars: Relevance of Interchangeability Designation to Clinics

In the USA, an approved biosimilar can be designated as "interchangeable." An interchangeable biosimilar "can be expected to produce the same clinical result as the reference product in any given patient" and demonstrates "for products that are administered more than once the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch" (Table 1) [16, 17, 97]. Where state law permits, this allows pharmacy-level substitution, meaning the interchangeable biosimilar may be substituted for the reference product without the need for a new prescription to be issued by the healthcare provider (HCP) who prescribed the reference product [17, 97]. A 2020 survey of physicians ($N = 602$) who prescribe biologics indicated that most (75%) were opposed to automatic substitution of biologics by pharmacists. The hesitancy of physicians toward automatic substitution could be due to a perceived lack of control over prescribing and patients' treatment [98, 99].

To date, only two ADL biosimilars in the USA have received interchangeability designation: Cyltezo ([adalimumab-adbm], Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA), and Abrilada (adalimumab-afzb) (Table 2) [46, 51]. Two ADL biosimilars have applications for interchangeability either submitted to (Hadlima [adalimumab-bwwd]) or under review with (Yuflyma [adalimumab-aaty]) the FDA

[48, 52], and two others are being evaluated in clinical studies designed to support an interchangeability designation (Amjevita [adalimumab-atto]; Hulio [adalimumab-fkjp], Mylan Pharmaceuticals Inc., Morgantown, WV, USA) (Table 2) [45, 49]. Lastly, an application for interchangeability included as part of the biologics license application for one additional proposed ADL biosimilar (AVT02) was accepted by the US FDA with anticipated approval in February 2024 [44].

The US FDA has issued draft guidance with recommendations on labeling for biosimilar and interchangeable biosimilar products [100]. Following this guidance, the agency recommends that labeling for both biosimilars and interchangeable biosimilars include a "biosimilarity statement" as all FDA-approved biosimilars must not have any clinically meaningful differences to their reference products, irrespective of their interchangeability designation [100]. The interchangeability designation is relevant at the point of pharmacy dispensing, i.e., an interchangeable biosimilar may be substituted for its reference product without the intervention of the prescribing HCP, where state law permits [17, 97]. Therefore, information about whether a biosimilar is licensed as an interchangeable biosimilar product is provided in the Purple Book, an online database of all licensed biologic products, including biosimilars and interchangeable biosimilars, that is accessible to pharmacists, HCPs, and the public [46, 100].

Reference ADL and both interchangeable ADL biosimilars are available for injection as a PFS or PFP. This would allow patients to continue using the same type of self-injection device after switching to an interchangeable ADL biosimilar. However, HCPs and advanced practice providers may need to consider how any differences between available devices could impact the injection experience for patients who are switched to an interchangeable ADL biosimilar with slightly different features than reference ADL (e.g., availability of smaller 29-gauge needle, whether it is manufactured with natural rubber latex, how it is supplied, whether the needle is attached, if the cap must be locked back on, etc.). Additionally, each time a patient switches from one device to another it would require a new technology visit and healthcare resources to educate the patient on how to use the device. Therefore, the feasibility of switching between different devices would also need to be considered.

Patient Support Programs

Attributes of the various ADL biosimilars will help to inform prescriber and patient choice of treatment. Resources and services provided through company patient assistance programs (PAPs) may also influence treatment choices. In the USA, companies that manufacture ADL products offer ADL-specific and/or non-ADL-specific PAPs to provide reimbursement or other financial assistance to patients for the cost of their medicine. In addition, some PAPs also provide resources to help patients understand the cost of their medicine; navigate insurance processes and provide information related to their insurance coverage; and help them understand their disease, treatment options, and prescribed medication. These programs have the potential to improve patient access to ADL products and will be an important factor for doctors to consider when discussing ADL treatment options with their patients.

CONCLUSIONS

ADL is an effective treatment for patients with chronic immune-mediated inflammatory diseases. Biologic drugs, such as ADL, are commonly administered via SC injection (by PFS or PFP), which can be associated with ISP. The extent of ISP during SC injection is influenced by various product-related factors, such as formulation, delivery volume, and device features (e.g., type and needle gauge size). Multiple ADL biosimilars that differ in delivery options, formulation, and dosing presentations are available to patients. As differences between product attributes can impact the injection experience and, by extension, treatment adherence and patient outcomes, various features of ADL biosimilars should be considered to better inform patient choice of treatment. Additionally, the impact of

interchangeable biosimilars and availability of PAPs that ensure access to medications are important factors for HCPs to consider when discussing ADL treatment options with their patients.

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Declarations

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