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ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iebt20

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To cite this article: Luca Stingeni, Silvia Ferrucci, Paolo Amerio, Caterina Foti, Cataldo Patruno & Giampiero Girolomoni (2025) Lebrikizumab: a new anti-IL-13 agent for treating moderate-to-severe atopic dermatitis, Expert Opinion on Biological Therapy, 25:1, 15-20, DOI: 10.1080/14712598.2024.2435427

To link to this article: https://doi.org/10.1080/14712598.2024.2435427

Published online: 06 Dec 2024.

EXPERT OPINION ON BIOLOGICAL THERAPY
2025, VOL. 25, NO. 1, 15–20
https://doi.org/10.1080/14712598.2024.2435427

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SPECIAL REPORT

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Lebrikizumab: a new anti-IL-13 agent for treating moderate-to-severe atopic dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a common chronic inflammatory skin disease. Moderate-to-severe AD severely affects patients' quality of life. New drugs selectively targeting molecular pathways involved in the pathogenesis of the disease led to a new era for the treatment of AD. However, the current available options are limited and do not completely fulfill patients' needs. Recently, lebrikizumab, a new humanized monoclonal antibody targeting IL-13, has been approved for treating moderate-to-severe AD.

Areas covered: By analyzing scientific literature reporting lebrikizumab phase 3 pivotal clinical studies and summarizing recent advances in AD pathogenesis, in this article we focused on the mechanism of action of lebrikizumab in comparison to other biologics used for treating AD and discussed clinical data that led to the approval of this biologic agent.

Expert opinion: Among biologics approved for moderate-to-severe AD, lebrikizumab is characterized by a unique mechanism of action and an attractive maintenance regimen, besides good efficacy and safety profiles. Moreover, clinical evidence suggests that patients naïve or pre-treated with other biologics and affected by AD localized in sensitive areas and by type 2 comorbidities might be successfully treated with lebrikizumab.

ARTICLE HISTORY
Received 7 November 2024
Accepted 25 November 2024

KEYWORDS
Atopic dermatitis; biologics; efficacy; interleukin-13; lebrikizumab; patient profile; safety

1. Introduction

Atopic dermatitis (AD) is the most common chronic relapsing inflammatory disease of the skin, with a prevalence around 20% of children and up to 10% of adults in countries with high income [1,2]. Italian epidemiological data reported a prevalence of 14.3% in pre-school children (0–5 years), 15–17% in schoolchildren (6–11 years), 8–13% in adolescents (12–17 years), and 8.1% in adults (18–65 years) [3–5]. Additionally, AD is not uncommon in the elderly population, reaching up to 11.6% of older adults (75–99 years) in the UK [6]. The pathogenesis of AD is characterized by an interaction of epidermal barrier dysfunction, skin microbiome imbalance and immune dysregulation, primarily driven by type 2 inflammation [2,7]. Interleukin (IL)-4 and IL-13 play a key role in this process, also contributing directly to signs and symptoms [8]. Although AD pathogenesis is mainly characterized by type 2 inflammation, other immune pathways have been involved in the process (their description is beyond the aim of this article) [2]. Targeting IL-4 and/or IL-13 with monoclonal antibodies has been demonstrated a successful therapeutic strategy: dupilumab (anti-IL-4 receptor [R] α) and tralokinumab (anti-IL-13) were approved by the European Medicines Agency (EMA) in 2017 and 2021, respectively [9,10]. In November 2023, lebrikizumab, a humanized IgG4 monoclonal antibody targeting IL-13, was approved by EMA [11].

1.1. Atopic dermatitis and IL-13: mechanism of action of lebrikizumab

Regarding type 2 inflammation, new evidence highlighted that IL-4 is mainly involved in central processes, such as humoral immunity regulation (including IgE switching), while IL-13 has a major role at the tissue level, driving cutaneous inflammation [12–14]. This hypothesis is supported by data showing a higher expression of IL-13 compared to IL-4 (which turned to be undetectable or low expressed) in AD lesional skin. In addition, IL-13 expression has been demonstrated to correlate with disease severity [13], suggesting that AD is mainly an IL-13-driven disease.

Both IL-4 and IL-13 are known to interact with IL-4Rα, suggesting a possible mechanism of redundancy aimed to guarantee immune defense. IL-4 can bind the type I receptor consisting of IL-4Rα and the γc subunit, while both IL-4 and IL-13 are able to bind the type II receptor consisting of IL-4Rα and IL-13Rα1. Additionally, IL-13 can bind IL-13Rα2, a decoy receptor known to contribute to internalization of IL-13 [13]. Among biologics, dupilumab binds IL-4Rα of the type I and type II receptors inhibiting both IL-4 and IL-13 signaling, while tralokinumab binds IL-13 inhibiting its interaction with both IL-13Rα1 and IL-13Rα2. Conversely, lebrikizumab binds IL-13 inhibiting only IL-4Rα/IL-13Rα1 heterodimerization, while allowing the interaction of IL-13 with IL-13Rα2 and consequently

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Article highlights

- Lebrikizumab is a new humanized IgG4 monoclonal antibody targeting IL-13 by inhibiting IL-4Rα/IL-13Rα1 heterodimerization, while allowing its internalization through IL-13Rα2, and approved for the treatment of moderate-to-severe AD in adults and adolescents eligible for systemic therapy.
- Lebrikizumab joins the armamentarium of biologics for treating AD by adding a new effective mechanism of action and an attractive maintenance regimen.
- Patients naïve or pre-treated with biologics, with AD localized in sensitive areas and with type 2 comorbidities might be successfully treated with lebrikizumab.
- Considering lebrikizumab favorable safety profile, it might be suitable for treating AD also in frail patients such as the elderly.

leaving intact its endogenous regulation (Figure 1) [13,15]. IL-13Rα2 can be upregulated by IL-4 or IL-13 via IL-4Rα/IL-13Rα1, thus activating negative feedback capable of reducing extracellular IL-13. This mechanism is inhibited by tralokinumab, potentially allowing the persistence of IL-13 and consequently amplifying AD pathological process. Additionally, *in vitro* results showed a higher binding affinity, slower binding dissociation rate and higher potency of lebrikizumab compared with tralokinumab [16].

1.2. Lebrikizumab indication and dosage

Lebrikizumab is indicated for the treatment of moderate-to-severe AD in adults and adolescents ≥12 years (body weight ≥40 kg) eligible for systemic therapy. Lebrikizumab dosage includes treatment with 500 mg at weeks 0 and 2, followed by 250 mg every other week (Q2W) during the induction period of 16 weeks, and once clinical response is reached, a maintenance regimen of lebrikizumab 250 mg every fourth week (Q4W). Additionally, the Q2W regimen can be extended up to week 24 to improve the outcome of partial responders at week 16. Lebrikizumab is available as 250 mg/2 ml solution for subcutaneous injection in pre-filled syringe or pre-filled pen [17].

2. Pivotal clinical trial designs and outcomes

The efficacy and safety of lebrikizumab in adults and adolescents with moderate-to-severe AD were evaluated in four phase 3 clinical pivotal studies: ADvocate1, ADvocate2, ADhere and ADore [18–21]. The ADvocate studies were two identical 52-week randomized, double-blind, placebo-controlled trials [18,20]; ADhere was a 16-week, randomized, double-blind, placebo-controlled study [21]; and ADore was a 52-week, open-label, single-arm study [19].

AD patients were treated with lebrikizumab following the indicated dosage during the induction period (16 weeks) or with placebo (2:1 ratio in randomized studies). In the ADvocate studies, patients responding to lebrikizumab 250 mg at week 16 were re-randomized (2:2:1 ratio) to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W, or placebo Q2W (lebrikizumab withdrawal) up to week 52 [17,18]. In the ADhere study patients also received concomitant topical corticosteroids (TCS) [17,21]. In the ADore study, after induction, patients received 250 mg lebrikizumab Q2W up to week 52 [19].

The main primary and secondary endpoints of the ADvocate1, ADvocate2, and ADhere studies are listed in Table 1 [17,18]. The ADore study enrolled only adolescent patients, and, since it is a safety study, the primary endpoint was the percentage of patients that discontinued the study treatment because of adverse events (AEs), while secondary efficacy endpoints included Eczema Area and Severity Index (EASI)-related and quality of life (QoL) measurements at week 52 [19].

As shown in Table 1, the ADvocate studies reported that significantly higher percentages of patients treated with lebrikizumab reached Investigator's Global Assessment (IGA) 0 or 1 and 75% reduction from baseline in the EASI (EASI-75) responses compared with the placebo groups at week 16 [20]. Additionally, ADvocate1 reported a reduction in the Pruritus Numerical Rating Scale (P-NRS) score ≥ 4-points from baseline in 45.9% of the patients in the lebrikizumab group compared with 13.0% of those in the placebo group ($p < 0.001$), while in ADvocate2, the corresponding percentages were 39.8% and 11.5% ($p < 0.001$) [20]. In ADvocate1, 6.1% of patients treated with lebrikizumab reported a reduction in the P-NRS score ≥ 4-points from baseline at week 2, as compared with 0.9% of those in the placebo group ($p = 0.02$); in ADvocate2, the corresponding percentages were 3.6% and 0.7% (not statistically significant) [20]. In addition, in ADvocate1 39.0% of patients

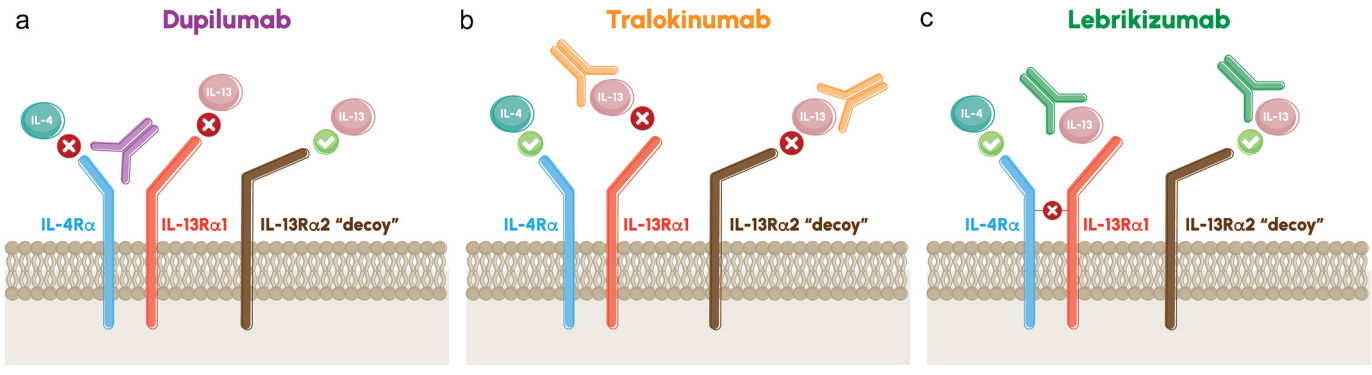

Figure 1. Anti-IL-4 and -13 mechanisms of action. (a) Dupilumab binds IL-4Rα inhibiting both IL-4 and IL-13 signaling [38]. (b) Tralokinumab binds IL-13 inhibiting its interaction with both IL-13Rα1 and IL-13Rα2 [31]. (c) Lebrikizumab binds IL-13 inhibiting IL-4Rα/IL-13Rα1 heterodimerization, while allowing the interaction of IL-13 with IL-13Rα2 (decoy receptor) [17]. Schematic illustration of lebrikizumab mechanism of action redrawn and modified from Moyle, Bieber, and Bernardo [13,15,39].

Table 1. Main efficacy data resulting from RCT of lebrikizumab in the treatment of moderate-to-severe AD.

	ADvocate1		ADvocate2		ADhere		ADore
Week 16	LEB	PBO	LEB	PBO	LEB+TCS	PBO+TCS	LEB
N. of patients	283	141	281	146	145	66	206
IGA score of 0 or 1 with reduction of ≥ 2 points from baseline (%)	43.1***	12.7	33.2***	10.8	41.2*	22.1	46.3
EASI-75 response (%)	58.8***	16.2	52.1***	18.1	69.5***	42.2	73.2
Pruritus NRS ≥ 4-point improvement (%)	45.9***	13.0	39.8***	11.5	50.6*	31.9	–
DLQI (Adults) ≥ 4-point improvement (%)	75.6***	33.8	66.3***	33.6	77.4*	58.7	−6.9[a]
	ADvocate1 and ADvocate2 (pooled)						
Week 52	PBO[e] (LW)	LEB Q4W	LEB Q2W				
N. of patients	60	118	113		–	–	–
IGA 0 or 1 (%)[b]	47.9	76.9**	71.2		–	–	62.6[f]
EASI-75 (%)[c]	66.4	81.7*	78.4		–	–	81.9[g]
Pruritus NRS ≥ 4-point improvement (%)[d]	66.3	84.7	84.6		–	–	–

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus placebo.
[a]The mean change in DLQI score from the baseline.
[b]Subjects with IGA 0/1 with a ≥ 2-point improvement from baseline at week 16 who continued to exhibit IGA 0/1 with a ≥ 2-point improvement at week 52.
[c]Subjects who achieved EASI-75 at week 16 and continued to exhibit EASI-75 at week 52.
[d]The percentage is calculated relative to the number of subjects with a baseline Pruritus NRS ≥ 4.
[e]Patients responding to lebrikizumab 250 mg Q2W at week 16 (IGA 0 or 1 or EASI 75) and re-randomized to placebo.
[f]% of patients that reached EASI-75 at week 52.
[g]% of patients that IGA 0 or 1 at week 52.
–Data not available; DLQI: Dermatology Life Quality Index; LEB: lebrikizumab; LW: lebrikizumab withdrawal; NSR: Numerical Rating Scale; PBO: placebo.

treated with lebrikizumab reported a reduction in the Sleep-Loss Scale score ≥ 2-points from baseline at week 16, compared to 4.7% of patients in the placebo group ($p < 0.001$), while in ADvocate2 the corresponding percentages were 28.0% and 8.2% ($p < 0.001$) [20]. Importantly, a significant improvement in P-NRS from baseline has been reported as early as day 2 (ADvocate1) and day 10 (ADvocate2), as well as a significant improvement in Sleep-Loss Scale score from baseline since day 3 (both studies) [22]. Recently, a further analysis of ADvocate studies reported a higher proportion of Itch- and Sleep-Loss Scale-responders (defined on the basis of improvement of Itch-NRS and Sleep-Loss Scale score, respectively) showing a meaningful improvement in Dermatology Life Quality Index (DLQI) compared with non-responders. These data demonstrated that in patients with AD treated with lebrikizumab the improvement of itch and itch-determined sleep interference was associated with QoL improvement [23]. Finally, in ADvocate1 75.6% of patients treated with lebrikizumab reported an improvement in the DLQI score ≥ 4-points from baseline at week 16, compared to 33.8% of patients in the placebo group ($p < 0.001$), while in ADvocate2, the corresponding percentages were 66.3% and 33.6% ($p < 0.001$) [20]. Overall, these data demonstrated that lebrikizumab was an effective treatment in adult and adolescent patients with AD [20]. Importantly, most responders to lebrikizumab Q2W at week 16 continued to maintain a response at week 52 when receiving lebrikizumab Q2W or Q4W (Table 1) [18].

In the ADhere study, at week 16 a significantly higher percentage of patients treated with lebrikizumab + TCS reached IGA 0 or 1 and EASI-75 compared to patients treated with placebo + TCS (Table 1). Moreover, 50% of patients in the lebrikizumab group were TCS/TCI-free at the end of the study in contrast to patients treated with placebo [21]. Overall, this study demonstrated an improved outcome of patients with moderate-to-severe AD treated with lebrikizumab + TCS, an approach commonly used in clinical practice [21]. Importantly, the rates of response observed in ADhere were similar to those obtained with monotherapy (ADvocate1 and 2) [20,21], suggesting that TCS might be not necessarily required.

In the ADore trial, the administration of lebrikizumab (52 weeks) resulted in a low serious AE (SAE) frequency (2.4%) and low treatment discontinuation (2.4%). Treatment-emergent adverse events (TEAEs) were mainly non-serious, mild, or moderate, confirming the safety profile observed in prior trials [19]. Considering the efficacy endpoints at week 52, 62.6% of the patients achieved IGA 0 or 1, 81.9% of patients reached EASI-75, and an improvement from baseline has been observed in QoL endpoints [19].

3. Conclusion

Lebrikizumab is a new innovative biologic therapy for treating AD by adding a new effective mechanism of action and an attractive maintenance regimen. Clinical data demonstrated that lebrikizumab, as monotherapy or combined with TCS, is an effective and safe treatment for adult and adolescent patients with moderate-to-severe AD.

4. Expert opinion

Characteristics of patients that might benefit most from lebrikizumab treatment are worthy of discussion following the recent approval of this new anti-IL-13 agent. As previously described lebrikizumab was approved by EMA and FDA for treating moderate-to-severe AD in adults and adolescents ≥12 years with a body weight ≥40 kg eligible for systemic therapy [17,24]. On the basis of clinical evidence, in this section we aimed to analyze more in detail the patients' profile suitable for lebrikizumab treatment.

Based on the eligibility criteria of the ADvocate studies, suitable patient features include: moderate-to-severe AD, an history of inadequate response to treatment with topical

medications (or medically inadvisable use), and no prior treatment with dupilumab or tralokinumab [20]. Conversely, the inclusion/exclusion criteria of the ADhere and the ADore studies allowed to enroll patients pre-treated with biologics (after adequate washout). Although the proportion of patients previously treated with dupilumab and tralokinumab was relatively low in these trials, the overall responses at week 16 were similar to those reported in the ADvocate studies (Table 1) [19–21], and consequently we assume that prior therapy with biologics might not impact the efficacy of lebrikizumab.

As previously described, lebrikizumab demonstrated to be rapidly effective in treating itch and itch related sleep loss [20,22], consistently improving patients' QoL and itch consequences, e.g. sleep loss and work absenteeism.

AD localization in sensitive areas, such as the face, scalp, neck, hand, and genitalia can be challenging and significantly affecting patients' QoL [25]. A post hoc analysis of the ADvocate studies confirmed that lebrikizumab monotherapy significantly improved EASI across all body regions (head and neck included) [26].

Multiple articles have reported the association between AD and other atopic conditions (such as asthma, rhinoconjunctivitis, and chronic rhinosinusitis with nasal polyps) [27,28]. This suggests the potential for biological therapies to ideally target both AD and the various type 2-related comorbidities. Considering IL-13 contribution to the pathophysiology of different type 2 conditions, its inhibition might be sufficient to control AD in patients with such comorbidities. Importantly, a recent post hoc analysis of the LAVOLTA I, LAVOLTA II, and ACOUSTICS studies, analyzing the rate of asthma exacerbations (defined as any new or increased asthma symptoms leading to systemic corticosteroids' administration or to hospitalization) as well as FEV_1 change from baseline, demonstrated that lebrikizumab significantly reduced asthma exacerbations in patients with elevated eosinophils, elevated FeNO and prior exacerbations [29,30], suggesting the potential efficacy of this biologic agent for treating asthma in AD patients.

Once clinical response is achieved following induction with Q2W administration for 16 weeks, lebrikizumab maintenance therapy is based on Q4W administration [17], considerably reducing administration burden for patients, positively impacting their treatment comfort and compliance. Additionally, as previously described, the Q2W regimen can be extended up to week 24 to potentially improve the outcome of partial responders at week 16 [17]. Once the response at week 16 is evaluated, lebrikizumab dosage offers a relatively large window (8 weeks) of flexibility in which clinicians can define the administration regimen (Q2W or Q4W) at their discretion. In addition, in patients experiencing a prior dupilumab failure, lebrikizumab maintenance therapy based on Q4W regimen might lead clinicians to select this biologic agent rather than tralokinumab, considering that the probability of maintaining clear or almost clear skin with tralokinumab may be lower with Q4W dosing [31].

An integrated analysis of lebrikizumab safety profile at week 16 including data from eight clinical trials concluded that the frequency of TEAEs was similar among different treatment groups (lebrikizumab and placebo), mostly non serious, mild, or moderate in severity, and rarely driving to treatment discontinuation. The lebrikizumab safety profile was consistent among the analyzed clinical trials regardless TCS use in both adults and adolescents, showing overall a positive benefit/risk profile [32]. In the ADvocate 1–2 and ADhere studies, conjunctivitis was among the most commonly reported TEAEs in the lebrikizumab arm at week 16 (frequency of 7.4%, 7.5%, and 4.8% respectively), mostly mild or moderate, and with minimal impact on treatment discontinuation [20,21]. Importantly, a longer lebrikizumab exposure (up to week 52) did not increased the incidence of conjunctivitis or other meaningful adverse events [18]. In addition, in the ADore study, protocol-defined AEs of special interest included the conjunctivitis cluster (allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis and giant papillary conjunctivitis) that was reported in 6.8% of the patients at week 52 [19]. Comparing the rate of conjunctivitis using different biologics highlighted a slightly higher incidence in patients treated with dupilumab compared to tralokinumab, suggesting that a therapy targeting only IL-13 might result in a lower risk of this event [33]. To better investigate the onset of conjunctivitis in clinical practice, we suggest AD patients should be evaluated by ophthalmologists before starting a therapy with any biologics approved for treating AD, relying on a multidisciplinary approach for managing these events. Moreover, in the ADvocate 1–2 and ADhere studies at week 16, and in the ADore study at week 52, among AEs of clinical interest reported in the lebrikizumab arm compared with placebo should be mentioned infections (21.6% vs 19.9% in ADvocate1, 23.1% vs 20.7% in ADvocate2, 16.6% vs 13.6% in ADhere, and 35.9% in ADore, respectively) as well as eosinophilia (0.4% vs 2.1% in ADvocate1, 1.1% vs 0% in ADvocate2, 0.7% vs 0% in ADhere, and 3.9% in ADore, respectively) [19–21]. Overall, an analysis of TEAEs of facial, head and neck erythema including four clinical studies did not show differences between lebrikizumab and placebo groups [26]. In addition, a low percentage of patients receiving lebrikizumab experienced injection site reactions, with a higher proportion reported in the lebrikizumab group compared with placebo, 2.6% and 1.5% respectively [32]. The favorable safety profile of lebrikizumab suggests that this biologic agent might be also suitable for treating frail patients such as the elderly, often in the presence of concomitant comorbidities and multiple therapies [34].

The evidence- and consensus-based European guideline (EuroGuiDerm) for the management and treatment of patients with AD was published in 2022 before approval of lebrikizumab. Consequently, this guideline provides recommendations only for dupilumab and tralokinumab as biologics in patient who are candidates for systemic therapy [35]. In addition, the Italian version of the EuroGuiDerm has been recently updated including lebrikizumab indications and dosage, reflecting EMA approval as well as the Italian Medicines Agency (AIFA) marketing authorization [36,37]. The introduction of lebrikizumab, as a new therapeutic option for treating moderate-to-severe AD, provides clinicians an additional efficient and safe biologic agent potentially able to fulfill patients' unmet needs, such as itch relief and skin clearance. In particular, lebrikizumab treatment might be beneficial in patients naïve or pre-treated with other biologics, with AD localized in sensitive areas, and with type 2 comorbidities. Nevertheless, further evidence in clinical practice is needed to validate the effectiveness of lebrikizumab in patient subpopulations.

Funding

Almirall S.p.A. Italy sponsored the editorial assistance for the writing and had no role in content of the manuscript.

Declaration of interest

L Stingeni received personal fees from and acted as Principal Investigator for AbbVie, Almirall, Eli Lilly, Leo Pharma, Novartis, Pfizer, Sanofi. S Ferrucci served as advisory board member, principal investigator in clinical trials and speaker for Almirall, AbbVie, Amgen, Leo Pharma, Galderma, Eli Lilly, Novartis, Pfizer, Sanofi. P Amerio has received honoraria for speeches and advisory board from: AbbVie, Almirall, Eli Lilly, Novartis, Galderma, Amgen, Pfizer. C Foti has received honoraria for speeches and advisory board from: AbbVie, Almirall, Eli Lilly, Novartis, Amgen, Pfizer, Sanofi, Incyte. C Patruno received personal fees form AbbVie, Almirall, Amgen, Eli Lilly, Galderma, Leo Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi. G Girolomoni has received personal fees from AbbVie, Almirall, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Pierre Fabre, Samsung bioepis and Sanofi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosure

Peer reviewers on this manuscript have received an honorarium from *Expert Opinion on Biological Therapy* for their review work. A reviewer on this manuscript has disclosed funds and honoraria from Eli Lilly. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

Conceptualization: L Stingeni and G Girolomoni. Literature analysis: All authors. Writing, reviewing and editing: All authors.

Acknowledgments

Guido Gambara, Medical Writer at PharmaLex Italy S.p.A.

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