SKIN

BRIEF ARTICLE

Efficacy and Safety of Tralokinumab in US Adults with Moderate-To-Severe Atopic Dermatitis: A *Post-hoc* Analysis of ECZTRA3

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ABSTRACT

Background: Tralokinumab, a monoclonal antibody that specifically neutralizes interleukin (IL)-13, is approved for the treatment of adults with moderate-to-severe atopic dermatitis (AD). Tralokinumab was studied in ECZTRA3 (NCT03363854), a randomized, double-blind, multi-national, placebo-controlled Phase 3 trial of tralokinumab in adults with moderate-to-severe AD.
Objective: We conducted a *post-hoc* analysis in the United States (US) subset of ECZTRA3 patients to inform healthcare practitioners and payers on the efficacy and safety of tralokinumab in the US setting.
Methods: Randomized patient received either 300 mg tralokinumab or placebo every 2 weeks (Q2W) in combination with TCS as needed for an initial 16 weeks. Thereafter, tralokinumab-treated patients continued with either Q2W dosing or Q4W+TCS for 16 additional weeks. Primary, secondary, and safety endpoints of the ECZTRA3 US subset were evaluated at 16 and 32 weeks per statistical analyses of the main study (previously published).
Results: The analytic population included n=63 and n=25, respectively, in the treatment and control arms. At Week 16, 37.1% tralokinumab+TCS vs 12.0% placebo+TCS reached Investigator's Global Assessment (IGA) 0/1 (nominal *P*=0.039); 56.5% of tralokinumab+TCS vs 24.0% placebo+TCS (nominal *P*=0.012) achieved the Eczema Area and Severity Index (EASI)-75. Secondary, patient-reported outcomes including itch score and health-related quality of life (HRQoL) were also improved at Week 16 versus baseline, more so for tralokinumab+TCS group. Tralokinumab was well tolerated, with an overall safety profile comparable to placebo.
Conclusions: Consistent with the full ECZTRA3 population, US patients with moderate-to-severe AD treated with tralokinumab+TCS as needed achieved greater symptom relief, reductions in disease severity and improvement of HRQoL than placebo+TCS, with comparable safety.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic, inflammatory skin disease characterized by the appearance of recurrent eczematous skin lesions and pruritus. AD is estimated to affect up to 20% of children and 3% of adults worldwide.[1] The epidemiology of AD varies regionally,[2] which has been partly attributed to environmental factors, socio-economics, urbanization, climate, diet, aeroallergens,[3] as well as inter-racial genetic susceptibility.[4,5]

Interleukin 13 (IL-13) is a key driver of underlying type 2 inflammation and skin-barrier dysfunction in AD,[6] hence US[7] and European[8] standard of care (SOC) includes use of both topical and systemic treatments, topical-corticosteroids (TCS), non-specific immunosuppressants, and biologic treatments targeting cytokines. Tralokinumab is a novel, fully human immunoglobulin G4 monoclonal antibody that binds to the IL-13 cytokine with high affinity, preventing IL-13 receptor interaction and subsequent downstream IL-13 signaling.[6] Tralokinumab is approved by the FDA for adults with moderate-to-severe AD whose disease is not adequately controlled by topical prescription therapies or when those therapies are not advisable.[9] ECZTRA3 (NCT03363854) is a pivotal, multinational, double-blind, randomized, placebo-controlled, clinical trial with combination topical corticosteroids (+TCS) as needed.[10]

In the United States, approximately 16.5 million adults have AD[11] and 6.6 million experience moderate-to-severe disease.[11] Given AD epidemiological specificities, evaluating treatment strategies warrants consideration of US-specific study populations. This *post-hoc* analysis assessed the efficacy and safety of tralokinumab in the US subset of ECZTRA3 patients.

METHODS

This was a double-blind, randomized, placebo-controlled 32-week trial conducted across 63 sites in Europe and North America (see Supporting Information).

After a 2–6-week screening period, patients were randomized 2:1 to subcutaneous tralokinumab 300 mg every 2 weeks (Q2W) +TCS as needed or placebo Q2W +TCS as needed, with a 600 mg of tralokinumab or placebo loading dose on day 0.[10] Primary endpoints included the Investigator's Global Assessment (IGA) score 0/1 (clear/almost clear) and Eczema Area and Severity Index (EASI)-75. Key secondary patient-reported outcome (PRO) endpoints included SCORing AD (SCORAD), Dermatology Life Quality Index (DLQI) scores and worst daily pruritus numerical rating scale (WDP-NRS) (weekly average). Statistical analyses followed the main analyses of ECZTRA3,[10] however, only nominal *P* values are reported for this post-hoc US subgroup evaluation.

Statistical Analysis

The difference in response rates between treatment groups was analyzed using the Cochran-Mantel-Haenszel test stratified by baseline severity.[12] For binary endpoints, patients who received rescue medication and patients with missing data were imputed as non-responders. The analysis of continuous endpoints used a mixed-effect model for repeated measurements with data collected after rescue medication use or permanent discontinuation of the investigational product treated as missing. We evaluated mean change from baseline (CFB) values using a restricted maximum likelihood-based

repeated-measures approach with the Newton Raphson Algorithm. The model included change from baseline as dependent variable, fixed categorical effects of treatment, baseline disease severity and treatment-by-week interaction, and continuous fixed effects of baseline value and baseline-by-week interaction. Within-patient errors were modelled by an unstructured covariance matrix. Denominator degrees of freedom were estimated using Kenward-Roger approximation. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 88 US patients were randomized to tralokinumab (n=63) or placebo (n=25), mean age 43 years-old, 69% female, and 55.6% White (**Table 1**). More patients on tralokinumab had moderate disease (65.1% with IGA-3) compared with placebo (48.0%); both groups otherwise had comparable baseline characteristics (**Table 1**).

More tralokinumab patients achieved IGA-0/1 (37.1% vs 12.0% placebo; *P*=0.039), and EASI-75 (56.5% vs 24.0% placebo; *P*=0.012) at Week 16 (**Figure 1**). Between group response rates differences were 22.1% (95% confidence interval [CI]: 4.1 - 40.0 *P*=0.039) for IGA-0/1 and 29.8% for EASI-75 (95%CI: 8.5 - 51.0; *P*=0.012) Tralokinumab patients also displayed a greater reduction in weekly average WDP-NRS ≥4 points at Week-16 (42.6%) than placebo (32.0%) with a between group difference of 9.6% (95%CI: –12.9 - 32.2; *P*=0.42) (**Figure 1**).

The mean (standard error [SE]) total Week-16 SCORAD total score reduced by 37.6 (2.62) points for tralokinumab versus 17.8 (4.19) for placebo (difference –19.8; 95% CI: –29.7 - [–9.9]; *P*<0.001) (**Figure 2**). Mean (SE) Week-16 DLQI total score was −12.7 (0.82) for tralokinumab compared with −7.9 (1.32) for placebo (difference 4.8; 95%CI: –7.9 - [–1.7]; *P*=0.003) (**Figure 2**).

Tralokinumab was well tolerated with an overall safety profile comparable to that of placebo from baseline to Week 16 with no serious AEs reported (**Table 2**).

DISCUSSION

This post-hoc analysis of US patients in the tralokinumab ECZTRA3 pivotal trial demonstrated that US patients treated with tralokinumab achieved significant symptom relief, reductions in disease severity, and improvement of health-related quality of life, with comparable safety versus placebo.

The US subgroup analysis was warranted given the racial diversity in the US subgroup (44.4% non-White) compared with the full ECZTRA3 patient population (24.2% non-White) and slightly lower baseline disease severity (IGA4 severe: 33.3% US patients vs 46.3% overall; median EASI score: 21.4 US patients vs 25.5 overall). During the initial 16-week trial period, compared with the overall ECZTRA3 population, the US tralokinumab subgroup showed numerically greater between-group differences versus placebo on Week-16 IGA-0/1 response, (22.1% US patients vs 12.4% overall), and EASI-75 (29.8% US patients vs 20.2% overall), driven by a lower placebo response. Between-group differences were also somewhat larger for the US subgroup than in the overall ECZTRA3 population for improvements on PROs (SCORAD: −19.8 US patients vs −10.9 overall; DLQI: –4.8 US patients vs −2.9 overall).[10] Finally, safety findings were consistent with the overall ECZTRA3 study population.[10] However, all

Table 1. ECZTRA3 US subpopulation patient baseline characteristics.

	Tralokinumab q2w + TCS as needed n=63	Placebo q2w + TCS as needed n=25	All randomized N=88
Age (years)			
Mean (±SD)	42.3 (17.6)	39.6 (17.3)	41.5 (17.4)
Sex, n (%)			
Female	41 (65.1)	13 (52.0)	54 (61.4)
Male	22 (34.9)	12 (48.0)	34 (38.6)
Race, n (%)			
White	35 (55.6)	6 (24.0)	41 (46.6)
Black or African-American	19 (30.2)	10 (40.0)	29 (33.0)
Asian	5 (7.9)	7 (28.0)	12 (13.6)
Other	4 (6.3)	2 (8.0)	6 (6.8)
Disease duration (years)			
Median [IQR]	25 [8.0 – 39.0]	22 [15.0 – 26.0]	24 [10.5 – 38.5]
Body surface area involvement			
Median [IQR]	33.0 [23.0 – 49.0]	26.0 [22.0 – 48.0]	31.5 [22.0 – 48.5]
IGA score n (%)			
Grade 3 (moderate)	41 (65.1)	12 (48.0)	53 (60.2)
Grade 4 (severe)	21 (33.3)	13 (52.0)	34 (38.6)
Disease severity indices			
EASI score (median [IQR])	20.5 [17.6 – 30.0]	24.5 [17.0 – 29.3]	21.4 [17.6 – 30.0]
SCORAD score (median [IQR])	62.5 [52.7 – 75.7]	67.0 [54.6 – 77.7]	63.9 [53.1 – 76.0]
Weekly average WDP-NRS score (median [IQR])	8.3 [7.1 – 9.0]	9.0 [7.1 – 9.2]	8.3 [7.1 – 9.1]
DLQI score (median [IQR])	18.0 [12.0 – 22.0]	23.0 [13.0 – 26.0]	18.0 [12.0 – 23.0]

Previous AD treatment, n (%)			
Any	63 (100)	25 (100)	88 (100)
Topical corticosteroids	63 (100)	24 (96.0)	87 (98.9)
Topical calcineurin inhibitors	20 (31.7)	7 (28.0)	27 (30.7)
Systemic steroids	39 (61.9)	15 (60.0)	54 (61.4)
Mycophenolate	2 (3.2)	1 (4.0)	3 (3.4)
Cyclosporin A	3 (4.8)	3 (12.0)	6 (6.8)
Methotrexate	5 (7.9)	4 (16.0)	9 (10.2)
Azathioprine	1 (1.6)	0	1 (1.1)
Phototherapy	12 (19.0)	5 (20.0)	17 (19.3)
History of allergy, n (%)			
Asthma	38 (60.3)	23 (92.0)	60 (56.8)
Food allergy	20 (31.7)	9 (36.0)	29 (32.9)
Hay fever	35 (55.6)	10 (40.0)	45 (51.1)

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; IQR, interquartile range; NRS, Numeric Rating Scale; SCORAD, SCORing Atopic Dermatitis; WA: weekly average; WDP, worst daily pruritus.

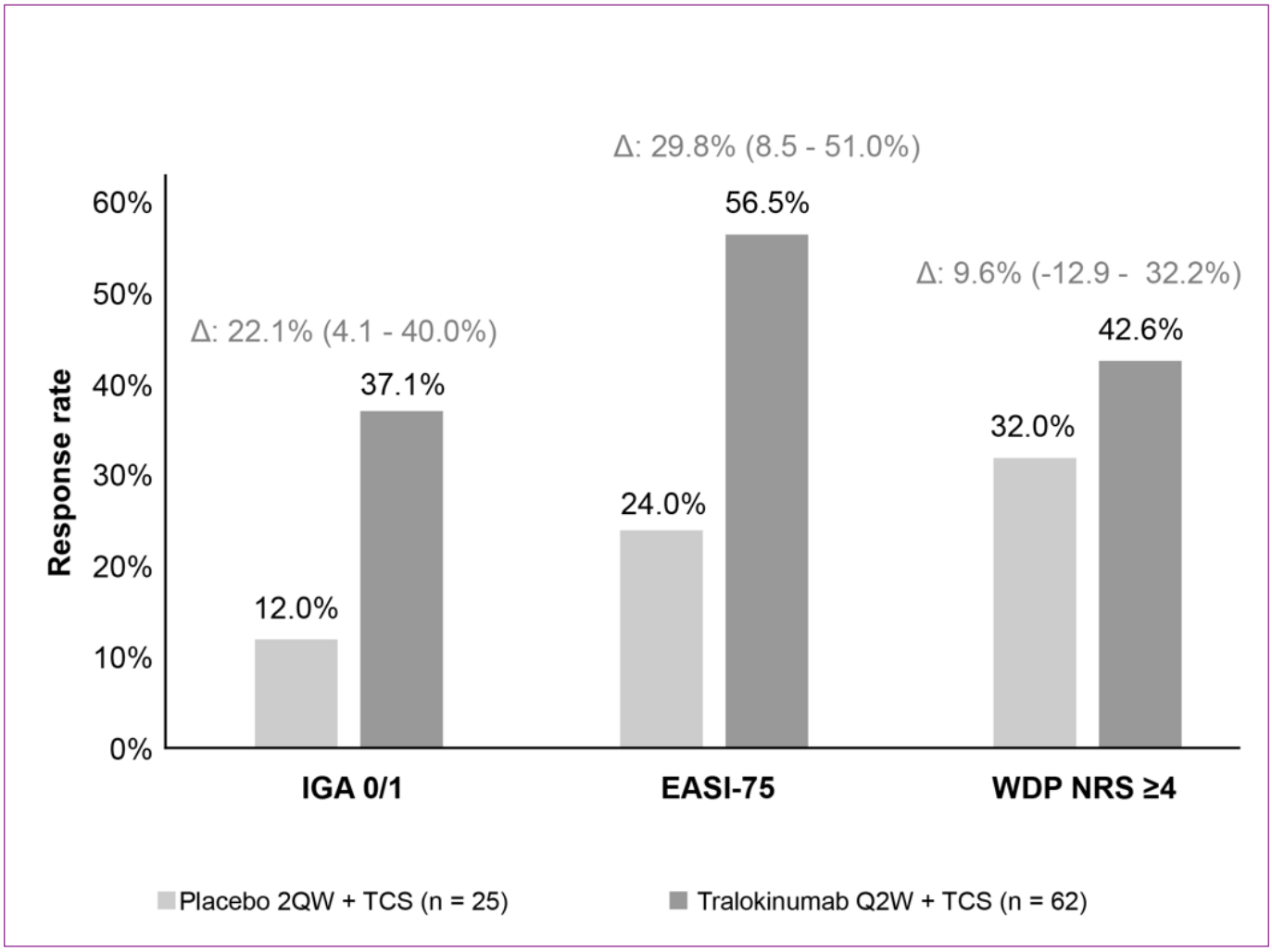

Figure 1. Week 16 response rates on IGA 0/1, EASI-75, NRS>=4 in ECZTRA3 US subpopulation.

Δ: Difference in response rates calculated based on stratification by the baseline IGA using the Cochran-Mantel-Haenszel test estimate.

EASI, Eczema Area and Severity Index; IGA-0/1, Investigator's Global Assessment score of 0 or 1; q2w, every 2 weeks; q4w, every 4 weeks; TCS, topical corticosteroids; WDP NRS, worst daily pruritus numeric rating scale.

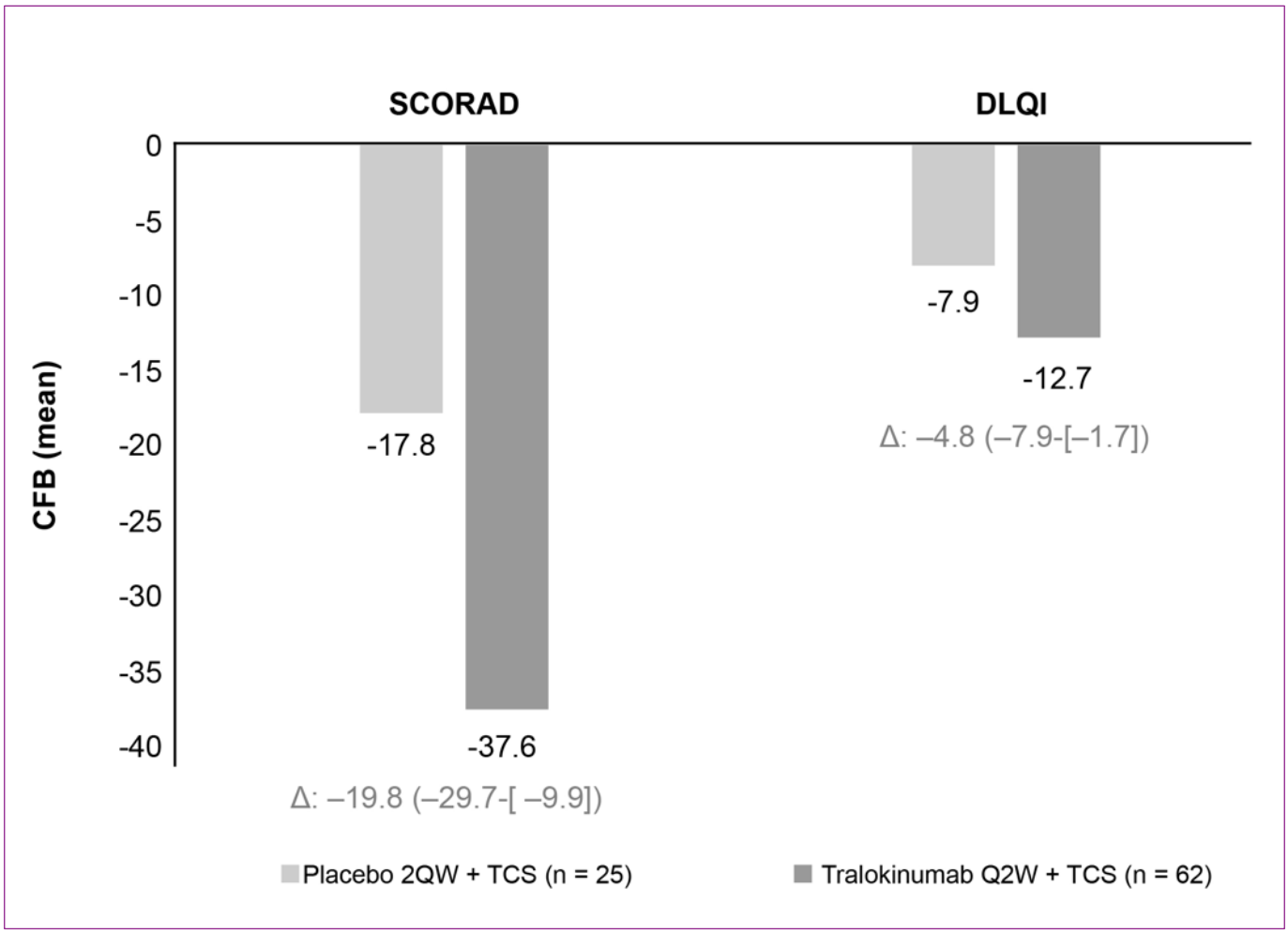

Figure 2. Week 16 change from baseline in SCORAD and DLQI adjusted means in ECZTRA3 US subpopulation.

Δ: Difference in total score and 95% confidence interval.

DLQI, Dermatology Life Quality Index; SCORAD, SCORing Atopic Dermatitis.

Table 2. Summary of adverse events during initial 16-week treatment and response rates at Weeks 16 in ECZTRA3 US subpopulation.*

	Tralokinumab q2w + TCS n=62; PYE=17.87	Placebo q2w + TCS n=25; PYE=7.5
Adverse events during initial 16 weeks of study:	**N (%)**	**N (%)**
At least one AE	40 (64.5)	16 (64.0)
At least one serious AE	0	1 (4.0)
AE leading to withdrawal from trial	2 (3.2)	0
Severity		
Mild	34 (54.8)	12 (48.0)
Moderate	11 (17.7)	6 (24.0)
Severe	0	1 (4.0)
Outcome		
Not recovered/Not resolved	13 (21.0)	3 (12.0)
Recovering/resolving	1 (1.6)	2 (8.0)
Recovered/resolved	38 (61.3)	13 (52.0)
Recovered/resolved with sequalae	1 (1.6)	0

*Among patients with IGA score of 0/1 at week 16 and EASI-75 among patients with EASI-75 at week 16.
AE, Adverse Event; PYE, Person Years of Exposure; q2w, every 2 weeks; TCS, topical corticosteroids

results must be considered in light of the limited size of the US subgroup.

CONCLUSION

In a subset analysis of US patients with moderate-to-severe AD from the pivotal trial, ECZTRA3, more patients treated with tralokinumab+TCS as needed achieved improvements in outcomes compared with placebo+TCS as needed. Tralokinumab+TCS as needed was also well tolerated. These results are consistent with the overall ECZTRA3 study population results.

Clinical trial number: NCT03363854

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Conflict of Interest Disclosures: Boni Elewski reports receiving honoraria as a consultant for Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, LEO Pharma, Lilly, Menlo Therapeutics, Novartis, Pfizer, Sun, Valeant (Ortho Dermatologics), and Verrica; and has received research funding from AbbVie, AnaptysBio, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Incyte, LEO Pharma, Lilly, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, Sun, Valeant (Ortho Dermatologics), and Vanda. **Matthew Zirwas** is a consultant, investigator, and/or speaker for AbbVie, All Free Care/Sun, Anaptys Bio, Arcutis, Bausch Health, Cara, Concert, Dermavant, Edessa Biotech, Eli Lilly and Company, EPI Health, Fit Bit, Galderma, Genentech, Incyte, LEO Pharma, Level-Ex, L'Oréal, LUUM, Menlo, Novartis, Oculus, Ortho Derm, Peloton, Pfizer, Regeneron, Sanofi, Trevi, and UCB, is a part owner of AsepticMD, and has worked with LEO Pharma and other companies with atopic dermatitis drugs that have received FDA approval or are expected to receive FDA approval in the next year. **Azra Kurbasic**, **Shannon Schneider**, and **Ami Claxton** are employees of LEO Pharma. **Jonathan I. Silverberg** reports personal fees from AbbVie, Afyx, AnaptysBio, Aobiome, Arena, Asana, Aslan, BioMX, Bluefin, Bodewell, Boehringer Ingelheim, Celgene, Connect Biopharma, Dermavant, Dermira, DS Biopharma, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Kymab, LEO Pharma, Luna, Menlo, Novartis, Pfizer, RAPT, Realm, Regeneron, and Sanofi Genzyme, grants and/or personal fees from Galderma, GlaxoSmithKline and Pfizer, and stock/stock options from AbbVie, Arcutis, and Eli Lilly.

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