We at AbbVie appreciate the opportunity to provide feedback on the Institute for Clinical and Economic Review's (ICER's) assessment of *JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis*: Draft Evidence Report published by ICER on May 14, 2021.¹

Executive Summary:

AbbVie's comments on the draft evidence report are largely focused on highlighting the salient issues related to incorrect data inputs and methodological errors which in turn are leading to faulty conclusions. We urge ICER to take immediate action to address these comments before the final report is released as an invalid assessment could lead to limiting patient access to treatments in atopic dermatitis, an area of high unmet need. AbbVie's response is summarized into three main sections: faulty conclusions, methodological errors, and major study limitations.

Faulty conclusions:

- The net health benefit of upadacitinib in AD is not "promising but inconclusive" compared to topical therapies or "insufficient" versus dupilumab as ICER concluded. Upadacitinib, in fact, is statistically significantly more efficacious on a range of measures than either placebo or dupilumab based on double-blind, randomized controlled trials and numerous network meta-analyses. The statistically significant and clinically meaningful superiority of upadacitinib versus placebo was shown in multiple randomized placebo-controlled trials (Measure Up 1, Measure Up 2, AD Up). ^{2,3} Similarly, the superiority of upadacitinib versus dupilumab was demonstrated in a large Phase III well-designed head-to-head clinical trial (Heads Up). In addition, the long-term safety of upadacitinib has been reported through study of up to 4.5 years of data across multiple clinical trials and indications.
- The conclusion that dupilumab dominates upadacitinib in the cost-effectiveness analysis lacks validity. One therapy dominates another in a cost-utility model when it produces more quality-adjusted life years (QALYs). Clinical efficacy is the main driver of QALYs gained, and as stated above, upadacitinib was shown to be superior to dupilumab in the head-to-head (Heads Up) clinical trial. In addition, ICER's own network meta-analysis (NMAs) show that when considering all evidence together upadacitinib 30mg is the most efficacious therapy in eight out of nine comparisons where ICER included upadacitinib.
- Finally, the resulting price at which upadacitinib is found to be cost-effective is biased by the various salient clinical and methodological limitations described herein this response letter.

Methodological errors:

The 1% discount rate applied to upadacitinib is erroneous and a major driver of high total cost
of upadacitinib treatment in ICER's assessment. The SSR Health data source should not be
used to estimate discounts to WAC prices, as clearly demonstrated by the evidence shared in
the later section of this response.

¹ ICER. JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value: Draft Evidence Report. May 14, 2021, Available at: https://icer.org/wp-content/uploads/2020/12/ICER Atopic-Dermatitis Draft-Evidence-Report 051421.pdf. ("Draft Evidence Report")

² Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *The Lancet*. 2021.

³ Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2021.

- The discontinuation rate for upadacitinib in the ICER's assessment are obtained from a
 Japanese rheumatoid arthritis study that is not representative of the atopic dermatitis
 population. AbbVie has recently provided confidential data to ICER from the Heads Up trial
 that show no difference in discontinuation rates for upadacitinib vs. dupilumab. Consistent
 with evidence in atopic dermatitis, the same discontinuation rate applied to dupilumab
 should also be applied to upadacitinib.
- ICER's assessment did not capture any economic savings of achieving EASI 90 vs 75 vs 50 scores in the cost-utility analysis. We have provided compelling evidence to ICER that is corroborated by previously published literature to show substantial cost savings associated with higher EASI scores that should be included in the final assessment.
- Methodological errors in ICER's NMA, including the omission of key clinical trial data, affected
 resulting transition probabilities generated for use in ICER's cost-effectiveness model. These
 incorrect transition probabilities for upadacitinib underestimate the true clinical benefit to
 patients relative to all other comparators in the model. This error primarily affects the EASI50 and EASI-90 transition probabilities for upadacitinib.

Major study limitations:

Some of the major limitations are listed in this executive summary. For a comprehensive list, please review the later sections of this response.

- ICER's base case cost-utility analysis does not fully capture the patient value of AD treatments (e.g., improvements in sleep, itch). It also does not capture any benefits of work productivity improvements or of EASI score improvements of less than 50. All these exclusions suggest a substantial portion of the value of AD treatments such as upadacitinib is not reflected in the economically justifiable price calculations or base case cost-utility analysis.
- Topical emollients are not standard of care for moderate to severe AD patients but rather supportive care at best, as assumed in the cost-utility and cost-consequence analyses. The terminology of SoC should be changed to supportive care for moderate to severe AD patients.
- NMA methods are not described sufficiently, and important Phase 3 trial data provided to ICER by AbbVie (e.g., Heads Up, the head-to-head Phase 3 trial of upadacitinib vs. dupilumab) are omitted from the analysis.

We are also deeply disappointed with ICER making public our confidentiality provided data to support the AD assessment. Specifically, on p. 312 of the Draft Evidence Report, ICER did not redact the productivity data reported in Table E4.1 that we provided them from the Measure Up 1 and Measure Up 2. This is a violation of ICER's guidelines that state, "[a]cademic-in-confidence data will be redacted from all external and public ICER documents until the earlier of: (a) publication or presentation of such data by the data owner or study investigators; (b) 18 months following the date of the public ICER meeting; (c) for reports that are not subject to a public meeting, 18 months following report publication." This carelessness adds to the challenges manufacturers such as AbbVie face when working with ICER to help improve the overall quality of the assessments being undertaken across the various therapeutic areas.

⁴ Institute for Clinical and Economic Review. Guidelines on ICER's Acceptance and Use of "In-Confidence" Data from Manufacturers of Pharmaceuticals, Devices, and other Health Interventions. https://icer.org/guidelines-on-icers-acceptance-and-use-of-in-confidence-data-from-manufacturers-of-pharmaceuticals-devices-and-other-health-interventions/. Accessed May 26, 2021.

Section 1: Faulty conclusions

<u>Faulty Conclusion # 1:</u> Despite 4 Phase II and 20 Phase III trials available for the assessed therapies in moderate to severe AD, with all but one of the Phase III trials receiving a USPSTF score of Good, ICER concluded that the net health benefit of upadacitinib (as well as all JAKs and tralokinumab) is "Promising but inconclusive" relative to the standard of care (Table 3.2, page 33).

AbbVie's position/proposed solution:

Upadacitinib has been evaluated for adults and adolescents with one Phase II and six Phase III trials. The Phase II trial assessed 167 patients (all adults) in a 16-week, double-blind, placebo-controlled trial and found a dose-response relationship for upadacitinib efficacy.⁵ Results for three randomized, doubleblind, placebo-controlled Phase III trials evaluating upadacitinib for adults and adolescents have been published: two monotherapy trials and one trial with topical corticosteroids. Measure Up 1 evaluated 847 patients (281 assigned to upadacitinib 15mg, 285 to upadacitinib 30mg, 281 to placebo) and Measure Up 2 evaluated 836 patients (276 assigned to upadacitinib 15mg, 282 to upadacitinib 30mg, 278 to placebo). Both studies found that the treatment was effective. ⁶ Upadacitinib with topical corticosteroids was evaluated in AD Up, which evaluated 901 patients (300 assigned to upadacitinib 15mg with TCS, 297 to upadacitinib 30mg with TCS, 304 to placebo with TCS) and found that upadacitinib with TCS was well tolerated and performed better than placebo with topical corticosteroids.⁷ One Phase III trial evaluated upadacitinib compared to dupilumab among adult patients: Heads Up (NCT03738397), with 689 enrolled. Two Phase III trials have not yet released results. Rising Up (NCT03661138), with 272 enrolled, is a study to evaluate safety of upadacitinib with topical corticosteroids in adolescent and adult patients. NCT04195698 is an open-label extension study of upadacitinib for adult patients with 485 enrolled.

AbbVie's upadacitinib trials had their randomization carried out appropriately, adequately concealed treatment allocation, included arms similar at the outset of the study in terms of prognostic factors, were blinded to the care providers, participants, and outcome assessors and did not have unexpected imbalances in dropouts between groups. An ITT analysis was included. As described above, these trials each found that upadacitinib was statistically significantly more efficacious across a variety of measures compared to placebo and dupilumab. Additionally, the safety data from these trials as well as up to 4.5 years long-term data other indications such as rheumatoid arthritis, psoriatic arthritis and axial

⁵ Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, Beck LA, Mohamed MF, Othman AA, Anderson JK, Gu Y, Teixeira HD, Silverberg JI. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020 Mar;145(3):877-884. doi: 10.1016/j.jaci.2019.11.025. Epub 2019 Nov 29. PMID: 31786154.

⁶ Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, Thaçi D, Chu CY, Hong HC, Kato N, Paller AS, Calimlim B, Gu Y, Hu X, Liu M, Yang Y, Liu J, Tenorio AR, Chu AD, Irvine AD. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021 May 20:S0140-6736(21)00588-2. doi: 10.1016/S0140-6736(21)00588-2. Epub ahead of print. PMID: 34023008.

⁷ Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Werfel T, Zeng J, Huang X, Hu X, Hendrickson BA, Ladizinski B, Chu AD, Silverberg JI. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021 May 20:S0140-6736(21)00589-4. doi: 10.1016/S0140-6736(21)00589-4. Epub ahead of print. PMID: 34023009.

spondyloarthritis show that upadacitinib's safety profile is similar to placebo. ICER's concern about the lack of additional long-term safety data sets an evidence standard such that no new therapy with a large, well-conducted clinical trials program could at most achieve a "Promising but inconclusive" rating from ICER.

We do not believe that the net health benefit of upadacitinib is inconclusive in AD as has been demonstrated through evaluation in the placebo-controlled trials. ICER should restate upadacitinib's comparative clinical evidence rating to "Superior." If ICER has a safety standard that differs from that of the FDA or EMA, it should clarify that standard.

<u>Faulty conclusion # 2:</u> ICER concluded dupilumab was more effective (dominant) compared to upadacitinib in its cost-utility analysis, despite there being a large Phase 3 head-to-head trial (Heads Up) that has demonstrated the superiority of upadacitinib over dupilumab

<u>AbbVie's position/solution:</u> These findings are not aligned with a large Phase III head-to-head trial Heads Up where upadacitinib showed superiority versus dupilumab for the primary endpoint and all ranked secondary endpoints (see table below).⁸

Table 1. Heads Up Results at Week 16*

	Dupilumab (300 mg) (n=344)	Upadacitinib (30 mg) (n=348)		
EASI 75ª	61%	71%		
EASI 90 ^b	39%	61%		
EASI 100°	8%	28%		
Percent Change from Baseline in Worst Pruritus NRS ^d	-49%	-67%		
Worst Pruritus NRS Improvement ≥4° (Dupilumab, n=336) (Upadacitinib, n=340)	36%	55%		

Table Source: AbbVie News Center Press Release (December 10, 2020) and AbbVie Data on File. ABVRRTI71468.

^{*} Primary endpoint was EASI 75 at week 16. Primary endpoint achieved a p-value of 0.006. EASI 90 and EASI 100 at week 16, percent change from baseline in Worst Pruritus NRS at week 16 and improvement in Worst Pruritus NRS ≥4 at week 16 were ranked secondary endpoints. All ranked secondary endpoints achieved p-values of <0.001. Not all ranked secondary endpoints are shown.

^a EASI 75 is defined as at least a 75 percent reduction in Eczema Area and Severity Index.

^b EASI 90 is defined as at least a 90 percent reduction in Eczema Area and Severity Index.

^c EASI 100 is defined as a complete reduction in Eczema Area and Severity Index.

^d Defined as percent change from baseline in Worst Pruritus Numerical Rating Scale [NRS].

e Worst Pruritus NRS improvement ≥4 is defined as an improvement (reduction) in Worst Pruritus NRS ≥4. The endpoint was analyzed for participants with pruritus NRS ≥4 at baseline.

⁸ AbbVie News Center. RINVOQ™ (upadacitinib) Achieved Superiority Versus DUPIXENT® (dupilumab) For Primary and All Ranked Secondary Endpoints in Phase 3b Head-to-Head Study in Adults with Atopic Dermatitis. <a href="https://news.abbvie.com/news/press-releases/rinvoq-upadacitinib-achieved-superiority-versus-dupixent-dupilumab-for-primary-and-all-ranked-secondary-endpoints-in-phase-3b-head-to-head-study-in-adults-with-atopic-dermatitis.htm." Published 2020. Accessed May 26, 2021.

ICER's model findings are also not aligned with ICER's own NMAs, which found that <u>in eight out of nine instances where</u> ICER included upadacitinib data its 30mg dose is the most efficacious therapy (Table 2). The only instance where ICER did not find upadacitinib to be the most efficacious therapy was in the EASI 50 monotherapy network where ICER only included Phase 2 data [which was miscited as Guttman Yassky et al. 2020, when it should have been cited as Guttman Yassky et al. 2018⁹] and failed to include the large Phase three trials placebo-controlled trials (Measure Up 1 and Measure Up 2¹⁰, and AD Up¹¹). Though ICER's NMA methods remain unclear, we expect that inclusion of all relevant trials would have shown that upadacitinib is the most efficacious therapy in all nine instances.

ICER's NMA shows that upadacitinib 30mg always performs better vs. dupilumab in terms of point estimates in nine out of nine comparisons, and upadacitinib 15mg usually performs better vs dupilumab, having a superior point estimate in six out of nine comparisons (Table 2). There are no randomized double-blinded controlled trial data, or any other data that we are aware of, that indicate that dupilumab or any other treatment is superior to upadacitinib in terms of efficacy.

Accordingly, ICER's model and conclusion that dupilumab is dominant to upadacitinib lacks face validity. ICER should carefully reevaluate the chosen inputs into cost-utility modeling and select the best available scientific evidence.

Table 2. ICER NMA endpoint rankings for UPA 30mg and 15mg versus other treatments

Figure	Endpoint and network	upadacitinib 30mg rank	upadacitinib 15mg rank	upadacitinib 30mg/15mg has superior point estimate in NMA versus dupilumab 300	Page in ICER Draft Evidence Report
Figure 3.1. NMA Results of EASI 75 in Placebo-controlled Monotherapy Trials in Adults	EASI 75 monotherapy	1 st	3 rd	Yes 30mg superior/yes 15 mg superior	27
Figure D2.2. NMA Results of EASI 50 in Placebo-controlled Monotherapy Trials	EASI 50 monotherapy	2 nd *	4 th *	Yes/no	97

⁹ Guttman-Yassky E, Anderson J, Pangan A, Silverberg JI, Thaçi D, Hong C. Primary results from a phase 2b, randomized, placebo-controlled trial of upadacitinib for patients with atopic dermatitis. In American Academy of Dermatology Annual Meeting 2018 Feb 16 (pp. 16-20).

¹⁰ Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. The Lancet. 2021.

¹¹ Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2021

Figure	Endpoint and network	upadacitinib 30mg rank	upadacitinib 15mg rank	upadacitinib 30mg/15mg has superior point estimate in NMA versus dupilumab 300	Page in ICER Draft Evidence Report
in Adults (Short-					
term)				Vastura	
Figure D2.3. NMA Results of EASI 90 in Placebo-controlled Monotherapy Trials in Adults (Short- term)	EASI 90 monotherapy	1 st	2 nd	Yes/yes	97
Figure D2.7. NMA Results of EASI 50 in Placebo-controlled Combination Trials in Adults	EASI 50 combination therapy	1 ^{st**}	2 nd **	Yes/yes	104
Figure D2.8. NMA Results of EASI 75 in Placebo-controlled Combination Trials in Adults	EASI 75 combination therapy	1 st	4 th	Yes/no	104
Figure D2.9. NMA Results of EASI 90 in Placebo-controlled Combination Trials in Adults	EASI 90 combination therapy	1 ^{st**}	4 th **	Yes/no	105
Figure D2.11. NMA Results of EASI 50 in Overall Trials in Adults	EASI 50 both networks	1 st *	3 rd *	Yes/yes	107
Figure D2.12. NMA Results of EASI 75 in Overall Trials in Adults	EASI 75 both networks	1 st	3 rd	Yes/yes	108
Figure D2.13. NMA Results of EASI 90 in Overall Trials in Adults	EASI 90 both networks	1 st	3 rd	Yes/yes	109

^{*} ICER only included Phase 2 trial data for upadacitinib; no Phase 3 data were included. See major limitations section.

^{**} ICER does not indicate source of the data. See major limitations section.

Note: ICER's NMA for combination therapy shows that no therapies are significantly different from placebo except for dupilumab in the EASI 90 comparison, which is contrary to the randomized controlled trial findings and a sign of a poorly fitting NMA. See major limitations section. Rankings indicate the order of most efficacious out of nine treatments in each analysis. ICER did not report NMA outcomes for upadacitinib in IGA or PP-NRS, despite there being Phase 3 data for these analyses.

<u>Faulty conclusion # 3:</u> ICER concludes that not only is upadacitinib not cost-effective relative to emollients but it is dominated by dupilumab (less efficacious and more costly) and thus, warrants a net price that is substantially discounted from the WAC price.

As noted above, the idea that dupilumab is more efficacious than upadacitinib is directly refuted by robust evidence from head-to-head clinical trials and numerous network meta-analysis conducted by ICER. Another driver of this result is that incorrect cost-utility modeling inputs such as the discontinuation rate used from a Japanese rheumatoid arthritis patients study (see below methodological error #2). In fact, we expect that when the various assumptions and methods are corrected, the ICER model will show that upadacitinib is not dominated by dupilumab and has a substantially lower incremental cost-effectiveness ratio relative to emollients. Thus, ICER's conclusions around what price upadacitinib would have to be to be cost-effective incorrect and substantially lower than what is supported by robust scientific evidence.

Section 2: Methodological errors

<u>Methodological error # 1:</u> The ICER methodology assumes a 1% discount off upadacitinib's wholesale acquisition cost (WAC) price in rheumatoid arthritis patients, whereas the next lowest discount used by ICER is 17%. The source for these prices and resulting discounts is SSR Health LLC – data that have several severe and well-documented limitations.

The limitations of the SSR Health data documented in the literature 12,13 include but are not limited to:

- (i) The Symphony Health data on unit sales, which are used in the net price calculation, are measured with error;
- (ii) There are discrepancies between when revenue and units sold are recorded especially at the time of product launch;
- (iii) Data on units per therapeutic course / annual supply are available only for select product-formulation combinations;
- (iv) Missing data due to companies not always reporting drug sales in SEC; and
- (v) In some cases, net price for a therapy as calculated by SSR Health LLC, exceeds its list price.

In addition, AbbVie has conducted an analysis of the data for upadacitinib in rheumatoid arthritis available through SSR Health LLC and has found key discrepancies which support the claim that these data are unreliable for determining upadacitinib's net price (and resulting discounting in the model). The figure below demonstrates findings on upadacitinib WAC and net price per unit from AbbVie's internal analysis of the SSR Health LLC data. The SSR Health LLC data does not accurately depict the net price of upadacitinib. In fact, in two quarters of 2020, our internal analysis of SSR Health LLC data found that their data depicted the net price of upadacitinib to be higher than the WAC price. Also, below is a statement from the SSR Health LLC regarding the use of their data to estimate net prices:

"Excluding the first 2 quarters of its commercial life (which we do for all products), SSR Health has generated 5 Rinvoq net price estimates. 3 of those estimates are computationally valid (i.e., Net < WAC), though subjectively appear too low (for example, they would barely cover an industry standard 2% prompt pay discount, let alone any other basic housekeeping, government mandated, or performance-based discounts). The other 2 net price estimates exceed WAC price by up to 16%, which is not credible. Taken together, this information suggests that the Rinvoq price estimates are unreliable, likely due to incomplete volume projections"

¹² Kakani P, Chernew M, Chandra A. Rebates in the pharmaceutical industry: Evidence from medicines sold in retail pharmacies in the us. National Bureau of Economic Research; 2020 Mar 12.

¹³ Sood N, Ribero R, Ryan M, Van Nuys K. The Association between Drug Rebates and List Prices. Los Angeles: University of Southern California Leonard D. Schaeffer Center for Health Policy and Economics. 2020 Feb 11;500.



Figure 1. SSR Health LLC data for upadacitinib WAC Price and Net Price from last two quarters of 2020

These are clearly nonsensical results and suggest upadacitinib price estimates generated using SSR Health LLC data are unreliable and lack credibility.

<u>AbbVie's position/proposed solution:</u> We believe that ICER should only use the WAC prices for all the assessed therapies in the base case analysis. This avoids any issues with differences in data collection on rebates that could bias comparison of the net results.

<u>Methodological error # 2:</u> ICER methodology used a discontinuation rate for upadacitinib in AD that is not representative of the population under assessment and disproportionately benefits dupilumab (over upadacitinib) in the cost-utility and economically justifiable price analyses.

Specifically, ICER relied on data from a Phase 2b/3 Japanese rheumatoid arthritis study studying patients who were on a stable dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs). We are not aware of published studies indicating that these patient populations are reasonably analogous, such that discontinuation rates for RA patients could be substituted for AD patients. This input is an important factor in the model. Use of data from this dissimilar population and indication to inform the discontinuation rate for upadacitinib in AD is misleading and results in a discontinuation rate approximately double that of other advanced therapies in the model.

AbbVie's position/proposed solution: AbbVie has recently confidentially shared additional discontinuation data of upadacitinib relative to dupilumab from the Heads Up clinical trial with ICER. These data compellingly demonstrate that upadacitinib has a lower discontinuation rate than dupilumab in moderate to severe atopic dermatitis patients. In addition, an internal AbbVie meta-analysis has found that upadacitinib's discontinuation rate due to adverse events is about in the middle of all the advanced therapies, and that its rate is not statistically different from that of any of the other advanced therapies for AD. For these reasons, use of discontinuation data for upadacitinib in AD from the Japanese RA study is misleading and should be reconsidered.

AbbVie's proposed solution is for ICER to use the same year 1 and year 2+ discontinuation rates for upadacitinib as those applied to dupilumab in the model. Given the findings from Heads Up, this approach will be conversative and still favors dupilumab. Alternatively, the maximum reasonable discontinuation rates used for upadacitinib should be averages of the discontinuation rates used for the

other active comparators in the model (not including SoC). Use of higher values of discontinuation rates than these for upadacitinib is erroneous and is not supported by the existing evidence in AD.

<u>Methodological error # 3:</u> ICER assessment did not capture any economic benefits to the healthcare system in their base case or full benefits to the patients of achieving higher clinical treatment targets in AD.

The ICER assessment does not differentiate between the cost savings among patients that achieve EASI 90 or 75 vs. EASI 50 scores. ICER also assumes a substantially lower cost of non-responder AD patients vs. what's observed in large national US claims datasets. In addition, ICER's cost-effectiveness analysis did not capture the patient and employer benefits of upadacitinib through outcomes such as work productivity improvement in the base case analysis that are critical for all the employer-sponsored health plans in the US.

<u>AbbVie's position/proposed solution:</u> AbbVie has provided cost data based on an analysis of the MarketScan data, showing differences in cost by severity (see table below). These cost estimates are similarly determined as the source relied on by ICER, Drucker et al. 2018,¹⁴ but provide more granularity that can be more easily mapped to the responder levels used by the model. Along with the data provided below in Table 3, we provided unadjusted results as well as our sample selection process to ICER to give them more detail on the methods utilized for the study. Table 4 shows the unadjusted and adjusted results presented by Drucker et al. 2018 for comparison (note, ICER relied on the unadjusted results instead of the adjusted results).

Table 3. Adjusted Direct Costs by AD Severity

	Non-AD Patients		Mild Patients		Moderate Patients			Severe Patients			
	Non-AD F		.,			IVIO		.5	Jevele r		
Consoliate	Mean	Standard	Mean	Standard	0	Mean	Standard	P-value	Mean	Standard	D. andrea
Covariate	iviean	error	iviean	error	P-value	iviean	error	P-value	iviean	error	P-value
Healthcare costs (Mean, SD)											
Total minus AD-Pharmacy	\$8,145.00	\$28.34	\$8,443.00	\$31.69	< 0.0001	\$9,571.00	\$98.64	< 0.0001	\$17,614.00	\$167.50	<0.0001
Pharmacy	\$1,303.00	\$3.69	\$1,421.00	\$4.09	< 0.0001	\$1,980.00	\$11.68	<0.0001	\$3,649.00	\$17.89	<0.0001
AD-related ^[2]	-	-	\$33.25	\$0.14	< 0.0001	\$105.20	\$0.60	< 0.0001	\$228.00	\$0.95	Ref. cat.
Non-AD related	\$1,300.00	\$3.67	\$1,377.00	\$4.03	< 0.0001	\$1,841.00	\$11.45	<0.0001	\$3,220.00	\$17.10	<0.0001
Inpatient	\$1,201.00	\$5.49	\$1,095.00	\$6.22	< 0.0001	\$1,118.00	\$15.94	< 0.0001	\$2,036.00	\$22.91	<0.0001
Outpatient	\$3,697.00	\$7.11	\$4,042.00	\$8.23	< 0.0001	\$4,378.00	\$21.77	<0.0001	\$6,849.00	\$31.66	<0.0001
Emergency room	\$240.60	\$0.75	\$311.40	\$0.97	< 0.0001	\$341.90	\$2.56	< 0.0001	\$533.30	\$3.49	<0.0001
Other	\$117.10	\$0.50	\$124.40	\$0.58	< 0.0001	\$131.20	\$1.47	< 0.0001	\$204.90	\$1.95	<0.0001
Healthcare resource utilization											
Outpatient visits	12.22	0.01	15.81	0.02	<0.0001	17.36	0.05	< 0.0001	23.36	0.06	<0.0001
Inpatient days	0.49	0.00	0.47	0.00	0.00	0.46	0.01	0.01	0.96	0.02	<0.0001
ER visits	0.42	0.00	0.57	0.00	<0.0001	0.64	0.00	< 0.0001	1.00	0.01	<0.0001
Other visits	0.79	0.01	0.89	0.01	< 0.0001	0.91	0.02	<0.0001	1.48	0.02	<0.0001
N (total)	2,039,388										

Notes

[1] Adjusted outcomes estimated using generalized linear models controlling for year of index date, age, gender, insurance type, employment type, AD comorbidities, and the Charlson comorbidity index [2] AD-related pharmacy costs are always zero in the non-AD patient cohort and therefore non-AD patients are excluded from those cost estimates.

¹⁴ Drucker AM WA, Li WQ, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *J Invest Dermatol.* 2017;137(1):26-30.

Table 4. Adjusted Direct Costs from Drucker et al. 2018, Table III

TABLE III. Annual health care utilization and costs among patients with atopic dermatitis stratified by disease severity

		Unadjusted		Adjusted*					
Resource category and metric	More severe AD (n = 3,849)	Less severe AD (n = 6,684)	Incremental difference	P value	More severe AD (n = 3,849)	Less severe AD (n = 6,684)	Incremental difference	P value	
Inpatient visit									
≥1 visit, no. (%)	587 (15.3)	700 (10.5)	5.2	<.0001	-	-	-	-	
No. of visits, mean (SE)	0.23 (0.68)	0.15 (0.55)	0.08	<.0001	0.36 (.05)	0.32 (0.05)	0.04 (0.07)	<.0001	
Length of stay (d), mean (SE)	0.7 (4.2)	0.4 (3.3)	0.3	<.0001	1.2(0.3)	1.0 (0.3)	0.2 (0.5)	<.0001	
Inpatient costs, mean (SE)	\$3,063 (\$362)	\$1,849.9 (\$82)	\$1,213	<.0001	\$5,325 (\$1,550)	\$4,392 (\$1,584)	\$933 (\$2,191)	<.0001	
Emergency department (ED)									
≥1 visit, no. (%)	1,008 (26.2)	1,309 (19.6)	6.6	<.0001	-	-	_		
No. of visits, mean (SE)	0.3 (0.7)	0.2 (0.6)	0.1	<.0001	0.5 (0.1)	0.4(0.1)	0.1 (0.1)	<.0001	
ED costs, mean (SE)	\$765 (\$63)	\$425 (\$82)	\$340	<.0001	\$988 (\$254)	\$661 (\$254)	\$328 (\$360)	<.0001	
Ambulatory visits									
≥1 visit, no. (%)	2,458 (63.9)	3,577 (53.5)	10.4	<.0001	-	-		-	
No. of visits, mean (SE)	3.7 (8.0)	2.4 (6.5)	1.3	<.0001	4.9 (0.6)	3.9 (0.6)	1.0 (0.9)	<.0001	
Ambulatory costs, mean (SE)	\$3,234 (\$254)	\$2,041 (\$82)	\$1,192	<.0001	\$5,170 (\$1,172)	\$4,232 (\$1,171)	\$938 (\$1,656)	<.0001	
Outpatient visits									
≥1 visit, no. (%)	3,837 (99.7)	6,659 (99.6)	0.1	.60	_	-	-	_	
No. of visits, mean (SE)	21.8 (21.3)	15.8 (16.0)	6.0	<.0001	30.1 (1.6)	23.8 (1.6)	6.3 (2.3)	<.0001	
Outpatient costs, mean (SE)	\$4,568 (\$296)	\$3,029 (\$82)	\$1,539	<.0001	\$6,444 (\$1,345)	\$5,116 (\$1,344)	\$1,328 (\$1,901)	<.0001	
Prescriptions filled									
≥1 prescription filled, no. (%)	3,756 (97.6)	6,380 (95.5)	2.1	<.0001	_	_			
No. of prescriptions filled, mean (SE)	21.8 (17.3)	15.2 (14.6)	6.6	<.0001	27.9 (1.3)	22.9 (1.3)	5.0 (1.9)	<.0001	
Prescription costs, mean (SE)	\$3,492 (\$196)	\$2,321 (\$82)	\$1,171	<.0001	\$4,333 (\$826)	\$3,397 (\$825)	\$936 (\$1,167)	<.0001	
Total costs, mean (SE)	\$15,122 (\$683)	\$9,667 (\$25,187)	\$5,455	<.0001	\$22,261 (\$3,016)	\$17,798 (\$3,013)	\$4,463 (\$4,263)	<.0001	

AD, Atopic dermatitis; SE, standard erro

However, ICER has not chosen to utilize the data we provided. We strongly suggest that ICER reconsiders this choice as patients who have achieved EASI 90 or above are going to look like a non-AD reference population in terms of cost, whereas someone achieving EASI 50, particularly if they were quite severe, would have costs like a patient with moderate severity.

Although ICER does present work productivity related costs in a sensitivity analysis, we feel strongly that this should be included in the base case as work productivity is a key outcome for employer sponsored health plans in the US. While for academic reasons work productivity is counted under "indirect costs" and hence only included in societal perspective analysis historically. The US healthcare system has evolved drastically over the decades since this framework was first proposed. Today majority of the insured US population is commercial, and employers deeply care about the quality of life of their employees as well their work productivity.

Furthermore, as noted in the executive summary, despite promising data confidentiality of clinical program results provided to ICER, ICER did not redact confidential data on WPAI from p. 312 of the report.

<u>Methodological error # 4:</u> Errors in ICER's NMA, including the omission of key clinical trial data, affected resulting transition probabilities generated for use in ICER's cost-effectiveness model.

In ICER's cost-effectiveness model, transition probability inputs are generated using outputs from ICER's NMA analysis. For this reason, errors in the NMA have a direct impact on the cost-effectiveness model. The resulting incorrect transition probabilities for upadacitinib underestimate the true clinical benefit to patients and consequently the model overestimates the ICER estimates of upadacitinib relative to all other comparators in the model. This error primarily affects the EASI-50 and EASI-90 transition probabilities for upadacitinib; these values in ICER's model are substantially lower than what they should be per the available robust clinical evidence.

^{*}Adjusted for age, gender, type of health insurance plan, region of residence, and atopic comorbidities (asthma, allergic rhinitis, chronic rhinosinusitis, conjunctivitis, nasal polyps, allergic urticaria, and esophagitis).

<u>AbbVie's position/proposed solution:</u> Please refer to the major limitations of the NMA analysis (major limitations #4 through #7) outlined in section 3 of this document. It is essential for ICER to address these limitations of the NMA analysis to ensure the correct transition probabilities for upadacitinib are estimated and ultimately used in the cost-effectiveness model.

Section 3: Major limitations

<u>Major limitation # 1:</u> ICER cost-effectiveness analysis did not capture the benefits of upadacitinib and other AD therapies in the improvement of the key patient symptoms such as pain, itch, and sleep.

IGA was a co-primary endpoint and was available in the trials of all compared therapies. Peak pruritus NRS (numerical rating scale) is the primary itch endpoint, which is the hallmark symptom of AD, and was available in the trials of all compared therapies. Both IGA and Peak pruritus NRS were excluded from ICER's NMA.

<u>AbbVie's position/proposed solution:</u> ICER should assess IGA and Peak pruritus NRS data and include analyses of these outcomes in its NMA. We believe that a robust cost-effectiveness analysis requires capturing these outcomes, potentially as responder thresholds in sensitivity analyses of the model. Including treatment specific utilities, as discussed below, is another option to capture the potential differences across treatments associated with these other outcomes.

If not, then ICER should state in the conclusions concerning cost-effectiveness and price threshold that they do not fully capture the value of upadacitinib in AD, as improvement in important patient symptoms such as sleep and itch were not captured in the cost-utility analysis.

<u>Major limitation # 2:</u> ICER model does not capture the benefits of achieving EASI improvements that are greater than zero but lower than 50%.

<u>AbbVie's position/proposed solution:</u> Although getting comparable utilities across all the trials would be difficult, one approach would be to include the marginal benefit estimated by each manufacturer for their therapy beyond what is explained by the model response states and adding that to the health state utilities currently employed by ICER.

<u>Major limitation # 3:</u> ICER has used the terminology of standard of care for topical emollients in the moderate to severe atopic dermatitis patients.

<u>AbbVie's position/proposed solution:</u> ICER should not use the terminology of standard of care for topical emollients in moderate to severe AD patients. Instead, ICER should consider the terminology of supportive care for topical emollients in moderate to severe AD patients. According to current guidelines for the evaluation and management of atopic dermatitis, topical emollients alone are for the basic management of AD; treatment for moderate to severe AD involves medical intervention. Specifically, guidelines recommend a step-care management of AD with basic maintenance management techniques alone limited to non-lesional and mild cases of AD. This is contrast to moderate to severe AD which requires maintenance treatment with basic management in addition to topical anti-inflammatory medications and/or systemic therapies.

¹⁵ Eichenfield LF, Ahluwalia J, Waldman A, Borok J, Udkoff J, Boguniewicz M. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. *Journal of Allergy and Clinical Immunology*. 2017;139(4, Supplement):S49-S57.

¹⁶ Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol.* 2018;120(1):10-22.e12.

Major limitation # 4: The ICER NMA is opaque on the methods and rationale for the choice of the model used. ICER states (page 91): "All network-meta-analyses (NMAs) were conducted in a Bayesian framework with random effects on the treatment parameters using the IndiRect NMA platform (CRG-EVERSANA, 2020TM). The outcomes were analyzed using a binomial likelihood and log link. The goodness of fit of the analyses with and without adjustment for differences in placebo arm response was assessed. We presented the results of the adjusted NMA model where it provided a better fit of the data." However, no fit statistics were provided, and ICER seems to have ruled out fixed effects models without explanation. ICER also does not provide the absolute risk rates (ARRs) and credible intervals (CrIs) for model inputs. We are concerned that the ARR CrIs for some random-effects models may not have face validity. SUCRA scores would also help explain the results.

<u>AbbVie's position/proposed solution:</u> ICER should present appropriate fit statistics for each NMA conducted. Specifically, ICER should submit the following information for each model:

- Number of MCMC chains used
- Total number of iterations and number of burn-in iterations used per chain
- Evidence assessed to concluded chain convergence (such as the final Potential Scale Reduction Factor value)
- The residual deviance (D res) compared to the number of datapoints informing the model
- The effective number of parameters (p_D)
- Deviance Information Criteria (DIC) (note: we can calculate this ourselves if they provide □_res and p_D, but good to see if their number match up)
- For random effects models, the prior distribution used and the posterior median and 95% credible intervals of the between-study standard deviation
- For adjusted models, the posterior median and 95% credible intervals of the adjustment parameter

ICER should also present ARRs with CrIs and SUCRA scores for each NMA conducted. Such information allows for a more complete validation of their models. It could deal with the specific concern that the CrIs of the ARRs lack face validity in some comparisons—a concern we have owing to the use of random effects models on relatively data-limited star-shaped networks.

Major limitation # 5: ICER's combination therapy analysis lacks face validity in that it differs from each of the randomized controlled trials used to populate it. ICER's NMA found no statistical difference between treatments (save for dupilumab at EASI 90) and placebo in the 'Placebo-controlled Combination Trials in Adults' network (Figures D2.7-D2.9). ICER claims this is due to "smaller effect size and smaller study populations." However, this analysis does not align with the findings of the individual RCT results. Upadacitinib, abrocitinib, and dupilumab each were found to be statistically significantly better than placebo in each of their combotherapy RCTs. This is evidence of a validity problem in ICER's NMA model selection or execution.

<u>AbbVie's position/proposed solution</u>: ICER should review these combination trials in adults NMA and identify a model fit that does not disagree with the individual RCT outcomes.

<u>Major limitation # 6:</u> ICER is using incomplete data for upadacitinib in its NMA. ICER'S NMA relies on Phase 2 data for upadacitinib exclusively for its EASI 50 analyses. This trial was relatively small in terms of sample size and sought to test different doses of upadacitinib. Phase 3 data would yield a more valid NMA. ICER also did not include outcomes for upadacitinib versus placebo for the IGA or PP-NRS endpoints, despite there being Phase 3 data for these analyses.

<u>AbbVie's position/proposed solution</u>: ICER should use the new published Measure Up 1 and Measure Up 2 publication, along with the AD Up publication. ^{17,18}

Major limitation # 7: ICER's documentation of which data it is using for its NMA and where those data are sourced is unclear. ICER's "Table D2.4. Key Outcomes in Placebo-controlled Combination Trials in Adults (Short-term)" indicates that EASI 50 and EASI 90 outcomes are not reported ("NR", page 102). However, ICER's NMA includes upadacitinib outcomes in its EASI 50 and EASI 90 combination therapy networks, per the figures "Figure D2.7. NMA Results of EASI 50 in Placebo-controlled Combination Trials in Adults" (page 104) and "Figure D2.9. NMA Results of EASI 90 in Placebo-controlled Combination Trials in Adults" (page 105). It is unclear what data ICER is using and how those data are sourced.

<u>AbbVie's position/proposed solution</u>: ICER should be clear as to which data it is using and where those data are sourced.

¹⁷ Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. The Lancet. 2021.

¹⁸ Reich K, Teixeira HD, de Bruin-Weller M, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet. 2021.





Electronic Submission

June 11, 2021

Institute for Clinical and Economic Review (ICER) 2 Liberty Square Boston, MA 02109

Dear ICER Review Panel:

Consumer Action and PIRG¹ are appreciative of the opportunity to provide comments on the Institute for Clinical and Economic Review's ("ICER") Draft Evidence Report regarding Atopic Dermatitis.

We work to rein in excessive drug prices and to promote patient choice. We appreciate the work of ICER, which seeks to define the cost-effectiveness of new therapies, and has successfully influenced several high-profile biopharma manufacturers' decisions to lower U.S. list prices.

We write these comments because we are concerned about the lack of meaningful patient choice resulting from drug manufacturers' use of anticompetitive contracting practices that restrict patients' access to new innovative therapies. Manufacturers with dominant drugs use financial incentives in the form of conditional rebates to negotiate preferred formulary access in the autoimmune therapeutic space, so this is relevant to ICER's current review. This contracting practice that keeps rival drugs in less preferred positions or even totally off of formularies is known as a rebate wall or trap and results in patients being denied access to lower cost and more efficacious drugs.

We want to frame the concerns for you regarding this anticompetitive practice from the consumer perspective so that the panel can understand that rebate walls have gained the attention of policy makers and antitrust enforcers; how rebate walls limit patient choice regardless of price; and why the panel should consider the competition and patient impacts of the rebate wall when it analyzes the cost effectiveness of each new drug for the atopic dermatitis market. Each patient experiences atopic dermatitis differently and there is no typical patient or treatment approach. Because of this, preserving treatment choice is critically important for patients.

ICER is currently conducting an economic evaluation of several JAK inhibitors and monoclonal antibodies seeking FDA approval to treat moderate to severe atopic dermatitis. Soon, JAK inhibitors including abrocitinib (Pfizer); baricitinib (Olumiant®, Eli Lilly); upadacitinib

¹ Consumer Action and Public Interest Research Group ("PIRG") are leading advocates for competitive markets, which benefit all consumers by maintaining lower prices and promoting innovation. They are public interest groups and advocates for competitive health care markets and leading advocates for consumers and patients who seek lower prescription drug prices.

(Rinvoq®, AbbVie); and ruxolitinib (Incyte Corporation) and a monoclonal antibody: tralokinumab (LEO Pharma) will be approved by the FDA and will be marketed to patients.

The key to the successful adoption of any of these newly launched prescription drugs by patients and healthcare providers is insurance coverage. If prescription drugs, particularly those as expensive as biologic treatments, are not widely reimbursed by insurance, patients will not have access to more affordable treatments. Rebate walls are likely to play a role in the adoption of some of these newly launched drugs. Specifically, our concern is that AbbVie uses a rebate wall to protect Humira and recently has been using rebate walls to help place Rinvoq on drug formularies to the detriment of rival drugs.

Because AbbVie will be entering the atopic dermatitis space with its new JAK inhibitor, we would like to highlight how AbbVie has used rebate walls in the autoimmune space. On May 15, 2021, congressional leaders sent a letter to the FTC requesting that the FTC investigate how AbbVie's use of rebate walls may have maintained Humira's market power by excluding rival drugs from preferred positions on drug formularies.² The letter further noted that "market experts have also raised concerns about AbbVie leveraging its market power to bundle rebates across indications to deny preferred positions on drug formularies to biosimilar and brand name rivals to Humira."³ These rebate walls are exclusionary contracting practices that AbbVie uses to limit the ability of rivals from gaining preferred formulary access or block them from getting on formulary at all.⁴ AbbVie provides conditional lucrative financial incentives to payors in the form of an "all or nothing" conditional sales volume-based rebate across Humira's ten indications in exchange for preferential formulary access and denying or limiting formulary access to a rival drug (i.e., step therapy). Rival drugs with only one indication and little to no patient volume cannot match the breadth of Humira's rebate so the payors are economically coerced to accept AbbVie's offer.

AbbVie's rebate walls foreclose competition⁵ and harm patients by increasing costs and restricting patient access to more effective and affordable prescription drugs.⁶ Dr. Wayne

https://jamanetwork.com/journals/jama/articleabstract/2753753); Commissioner Rohit Chopra, Federal Trade Commission, Dissenting Statement in the Matter of AbbVie, Inc. / Allergan plc (May 5, 2020) (online at www.ftc.gov/system/files/documents/public_statements/1574583/191-

https://www.businesswire.com/news/home/20201106005547/en/Let-My-Doctors-Decide-Announces-Expanded-

² Letter from Carolyn B. Maloney Chairwoman of the Committee of Oversight and Reform, Jerrold Nadler, Chairman of the Judiciary Committee, and David N. Cicilline, Chairman Subcommittee on Antitrust, Commercial, and Administrative Law Committee on the Judiciary to FTC Acting Chairwoman Rebecca Slaughter, May 18, 2021, p. 8 available at https://oversight.house.gov/sites/democrats.oversight.house.gov/files/2021-05-18.CBM%20Nadler%20DNC%20to%20Slaughter-FTC%20re%20AbbVie%20%28with%20enclosure%29.pdf.

³ *Id.* at p. 7 citing to Walid F. Gellad and Chester B. Good, Adalimumab and the Challenges for Biosimilars, Journal of the American Medical Association (Oct. 23, 2019) (online at https://jamanetwork.com/journals/jama/articleabstract/2753753); Commissioner Rohit Chopra, Federal Trade

⁰¹⁶⁹_dissenting_statement_of_commissioner_rohit_chopra_in_the_matter_of_abbvie-allergan_redacted.pdf).

4 Rebates are payments from drug manufacturers to PBMs and insurers. Although they may appear to have the

potential to lower the cost of drugs, a huge portion of them are pocketed by the PBMs and insurers.

⁵ David Balto, Drug Rebate Walls Should Be Dismantled by the FTC's Antitrust Arm, Stat News, December 4, 2018 available at https://www.statnews.com/2018/12/04/ftc-dismantle-drug-rebate-walls/.

⁶ Providers and patient groups have raised concerns about rebate walls. See Let My Doctors Decide Announces Expanded Patient Centered Principles and Issues Call to Action to Drive Access and Affordability, Millions of Americans Face Health Insurance Coverage Barriers; Formulary Contracting Increasingly a Concern for Patients and Doctors, November 6, 2020 (urging CMS, employers, insurers, and other decision-makers to adopt patient-centered principles that would eliminate rebate walls) available at

Winegarden, director of Pacific Research Institute's (PRI) Center for Medical Economics and Innovation, claims that rebate walls cause patients to suffer in the form of artificially inflated prices which result in higher coinsurance payments, or out of pocket expenses that are usually a percentage of the list price, as well as reduced choice. Dr. Winegarden calculates that ending rebate walls would save patients more than \$6,000 of out of pocket savings for expensive biologics like Humira that run approximately \$70,000 per year. Importantly, rebate walls cause patients to miss out on obtaining more effective treatments sooner by having to step through older incumbent drugs prior to using new more effective treatments. This raises the costs for patients and health plans because patients need to try older drugs and fail before gaining access to more effective and affordable treatments from the beginning.

AbbVie's rebate walls protect Humira and helped with the launch of two of its new **immunology drugs.** AbbVie's rebate wall involves the coupling of volume-based rebates across Humira's ten indications with penalty provisions, resulting in the withholding of hundreds of millions of dollars from payors that put rival drugs on their formularies. 9 On September 12, 2019, twelve consumer and public interest groups and four unions signed onto a letter to the FTC expressing concerns about the anticompetitive effects of the AbbVie-Allergan merger and identified AbbVie's use of rebate walls as a competitive concern. 10 AbbVie's rebate wall kept Humira in the preferred position on formularies while impeding the ability of new drugs indicated for moderate to severe psoriasis from obtaining the preferred position on formularies even though many of the new drugs are clinically superior and lower cost than Humira. 11 On May 5, 2020, FTC Commissioner Rohit Chopra raised concerns in his dissent of the FTC's approval of AbbVie's acquisition of Allergan that the FTC had evidence suggesting that AbbVie used its bargaining leverage and rebates on Humira to help with the launch of its new branded drugs. 12 Indeed, AbbVie used rebate walls based off of Humira's prescription volume to compel payors to put its new psoriasis drug, Skyrizi, in a preferred position on payors' drug formularies. 13 These arrangements also prevented these more efficacious drugs from being

<u>Patient-Centered-Principles-and-Issues-Call-to-Action-to-Drive-Access-and-Affordability;</u> see also Global Health Living Foundation's comments at the FTC/FDA Joint Biosimilars Workshop available at https://beta.regulations.gov/comment/FDA-2019-N-6050-0012.

⁷ Wayne Winegarden, Tearing Down Drug Rebate Walls Would Save Patients and Improve Healthcare Outcomes, Pacific Research Institute, December 9, 2020 available at https://www.pacificresearch.org/new-brief-tearing-down-drug-rebate-walls-would-save-patients-improve-health-care-outcomes/.

8 Id.

⁹ See, e.g., Citron Research, Citron Research Explains Why AbbVie is on its Way to \$60, July 24, 2018 available at https://citronresearch.com/wp-content/uploads/2018/07/Citron-Research-Explains-Why-AbbVie-is-on-its-way-to-60.pdf

¹⁰ Letter to FTC Chairman Simons regarding AbbVie's acquisition of Allergan, September 129, 2019 available at https://docs.wixstatic.com/ugd/1859d0 92f865639fc74293a62fef5c4fe1c62c.pdf.

¹¹ Joshua Cohen, Rebate Walls Stifle Prescription Drug Competition, Forbes, March 1, 2021 available at https://www.forbes.com/sites/joshuacohen/2021/03/01/rebate-walls-stifle-prescription-drug-competition/?sh=27056bf066ae.

¹² Commissioner Rohit Chopra, Federal Trade Commission, Dissenting Statement in the Matter of AbbVie, Inc. / Allergan plc (May 5, 2020) (online at www.ftc.gov/system/files/documents/public statements/1574583/191-

⁰¹⁶⁹_dissenting_statement_of_commissioner_rohit_chopra_in_the_matter_of_abbvie-allergan_redacted.pdf).

13 ZITTER HEALTH INSIGHTS, THE MANAGED CARE MESSAGE MONITOR: PSORIASIS DATA

SPOTLIGHT (June 2018), at 6. In June 2018, Zitter reported that "AbbVie continues to promote portfolio contracting opportunity for risankizumab [i.e., Skyrizi] that provides enhanced Humira rebates in exchange for exclusively preferring its pipeline agents".

placed on a preferential position on the formulary forcing patients to go through costly step therapy before having access to the most effective drug for their particular diagnosis. ¹⁴ Moreover, AbbVie's rebate wall has essentially been used to preserve formulary spots for both of its new drugs, Skyrizi and Rinvoq. ¹⁵

Federal Trade Commission Is Concerned About Rebate Walls

On May 28, 2021, the Federal Trade Commission (FTC) issued a report on rebate walls to Congress and committed to investigating exclusionary practices that "threaten to delay new entry" and "deny patients access to competing treatments." In its report, the FTC outlines the framework for a legal analysis of drug company rebate practices and noted that "a variety of stakeholders have identified rebate wall issues" and that "the Commission is closely attuned to pharmaceutical manufacturer contracting practices, including rebate strategies." Both FTC Chairwoman Rebecca Slaughter and Commissioner Rohit Chopra issued their own statements noting that the FTC needs to give more attention to rebate walls, but that the normal FTC investigatory process would likely take too long to avoid competitive harm in the near term. And, reportedly, the FTC has been investigating Johnson & Johnson's ("J&J") use of anticompetitive rebate walls to protect its blockbuster drug, Remicade, a drug used to treat rheumatoid arthritis, and to stifle the entry of Pfizer's biosimilar, Inflectra. So, the use of rebate walls is not limited to AbbVie. Others may be using the practice to stifle the entry of not just branded drugs, but for biosimilars and generics as well.

¹⁴ *Id.* A Blue Shield of California representative stated to Zitter that "he/she was 'dubious' of a portfolio contract for Humira in rheumatoid arthritis since AbbVie 'created the Humira contracting monster that shuts all competitors out' and is 'notorious for price increases'".

¹⁵ ZITTER HEALTH INSIGHTS, THE MANAGED CARE MESSAGE MONITOR: PSORIASIS DATA SPOTLIGHT (Mar. 2019), at 7. Prior to Skyrizi's launch, a payor, SelectHealth, told Zitter: "In terms of Humira, there would be increased rebates for ... place-holding for the future AbbVie product launches."

¹⁶ Federal Trade Commission Report on Rebate Walls, FTC, May 28, 2021 available at https://www.ftc.gov/system/files/documents/reports/federal-trade-commission-report-rebate-walls/federal-trade-commission-report-on-rebate-walls-pdf.

¹⁷ *Id*.

¹⁸ Statement of Acting Chairwoman Rebecca Slaughter Regarding the Commission's Report to Congress on Rebate Walls, May 28, 2021 available at

https://www.ftc.gov/system/files/documents/public_statements/1590532/statement_of_acting_chairwoman_slaughter_regarding_the_ftc_rebate_wall_report_to_congress.pdf; Statement of Commissioner Rohit Chopra Regarding the Commission's Report on Pharmacy Benefit Rebate Walls, May 28, 2021 available at

https://www.ftc.gov/system/files/documents/public_statements/1590528/statement_of_commissioner_rohit_chopra_regarding_the_commissions_report_on_pharmacy_benefit_manager.pdf; see also, Rohit Chopra June 1, 2021 tweet available at https://twitter.com/search?q=rebate%20wall&src=typed_query.

^{*}this link is to general twitter search for 'rebate wall' – Chopra's tweet is https://twitter.com/chopraftc/status/1399735809436160009.

¹⁹ Eric Sagonowsky, *J&J boasted about defending Remicade from biosims. Now it's under FTC investigation*, FiercePharma, July 30, 2019 available at https://www.fiercepharma.com/pharma/j-j-has-boasted-about-its-remicade-defense-and-now-it-s-under-ftc-investigation. In 2017, Pfizer sued J&J for its bundling practices. Pfizer v. Johnson & Johnson, et al, No. 17-cv-4180 (September 20, 2017).

²⁰ Scott Gottlieb, *Don't Give Up on Biosimilars—Congress Can Give Them a Boost*, Wall Street Journal, August 24, 2019 available at https://www.wsj.com/articles/dont-give-up-on-biosimilarscongress-can-give-them-a-boost-11566755042. He argued for the need to "stop branded drug companies from using 'rebates' to squelch competition from biosimilars...If there's one situation where rebates are anticompetitive, it's when they're being used to block competition from a low-cost generic."

Policy Makers Are Concerned About Rebate Walls

On September 17, 2019, nine Senators, including *then* Senator Kamala Harris, wrote a letter to the FTC regarding the AbbVie/Allergan merger and they recognized that rebate walls harm competition and reduce consumer choice. The letter noted that "rebate traps or rebate walls can have the effect of preventing alternative drugs, including more affordable biosimilars and generics, from competing." On June 10, 2020, Senators Klobuchar and Blumenthal as well as Congressmen Cicilline and Jeffries asked the GAO "to conduct an assessment of the prevalence of rebate traps in pharmaceutical markets and their effects on pharmaceutical pricing, competition, and innovation." They noted that rebate walls can "be used in harmful ways to strategically exclude competing products. So-called "rebate traps" (or "rebate walls") may stifle pharmaceutical competition and product development, potentially limiting patients' access to lower-cost generic drugs and biosimilars, as well as new innovative drugs." On July 17, 2020, the U.S. House Committee on Appropriations included language in its report accompanying H.R. 7668 urging "the FTC to prioritize investigations into manufacturers that erect rebate walls to block competition from new branded therapies, biosimilars, generics, and other innovative products."

Given AbbVie's history and the interest from policy makers and antitrust enforcers in its use of rebate walls, we are concerned that AbbVie could use rebate walls to advantage Rinvoq and disadvantage its rivals for the treatment of moderate to severe dermatitis. Accordingly, we hope that ICER's comparative value assessment of atopic dermatitis considers the market realities that rebate walls exist in the autoimmune space and how AbbVie's rebate wall could create barriers to more cost-effective therapies by foreclosing their access to drug formularies. The problem is that the most cost-effective products are unlikely to be available to patients if they cannot get on a drug formulary because of a rebate wall.

We sincerely appreciate your thoughtful consideration of the issues discussed in this letter.

If you have any questions regarding these comments, please contact David Balto at david.balto@dcantitrustlaw.com.

Respectfully submitted,

Consumer Action

PIRG

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²¹ Senator Klobuchar News Release, Klobuchar Leads Warning that Pharmaceutical Mergers May Threaten Drug Competition, Increase Prices and Reduce Patient Access, September 17, 2019 available at https://www.klobuchar.senate.gov/public/index.cfm/2019/9/klobuchar-leads-letter-warning-that-pharmaceutical-mergers-may-threaten-drug-competition-increase-prices-and-reduce-patient-access-to-essential-medications. ²² *Id.*

²³ Senator Klobuchar News Release, Klobuchar, Blumenthal, Cicilline, Jeffries Call on Government Accountability Office to Study Effects of "Rebate Traps" on Pharmaceutical Prices and Competition, June 10, 2020 available at https://www.klobuchar.senate.gov/public/index.cfm/2020/6/klobuchar-blumenthal-cicilline-jeffries-call-ongovernment-accountability-office-to-study-effects-of-rebate-traps-on-pharmaceutical-prices-and-competition.

²⁴ *Id.*

²⁵ FINANCIAL SERVICES AND GENERAL GOVERNMENT APPROPRIATIONS BILL, 2021 Report July 17, 2020, available at https://www.congress.gov/116/crpt/hrpt456/CRPT-116hrpt456.pdf.





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June 11, 2021

Submitted electronically to: publiccomments@icer-review.org Institute for Clinical and Economic Review (ICER) One State Street, Suite 1050 Boston MA 02109 USA

As the manufacturer of ruxolitinib cream, Incyte Corporation appreciates the opportunity to provide comment on ICER's Draft Evidence Report on JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis.

At Incyte, we take a science-first approach. Our research and development efforts in Dermatology leverage our knowledge of the JAK-STAT pathway to identify and develop topical and oral therapies with the potential to modulate immune pathways driving uncontrolled inflammation and help restore normal immune function.

We are sharing feedback, based on our deep understanding of JAK inhibition as well as the clinical evidence of ruxolitinib cream, to inform the evidence report.

I. Recommendation for consistent nomenclature of ruxolitinib:

An oral formulation of ruxolitinib is available in the United States, however the oral formulation is <u>not indicated</u>, nor being evaluated, for use in patients with atopic dermatitis. Therefore, we recommend that *ruxolitinib cream* is the preferred term, replacing *ruxolitinib* throughout the document.

Draft Evidence Report Text: Page 11, Paragraph 2: "While ruxolitinib also appeared to be more effective than a medium potency topical corticosteroid..."

Suggested revision: "While ruxolitinib <u>cream</u> also appeared to be more effective than a medium potency topical corticosteroid..."

II. Recommendation to change placebo to vehicle cream:

Phase 3 clinical studies evaluated ruxolitinib cream against vehicle cream. We recommend a global change throughout the document to replace "placebo" with "vehicle cream," for accuracy and consistency.

III. Recommendation to specify safety concerns related to oral JAK inhibitors



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When discussing important safety considerations of systemic JAK inhibitor therapies, we recommend the report specify *oral* JAK inhibitors consistently throughout the Evidence Report. We have identified 3 places where the change needs to be made.

Draft Evidence Report Text:

Page 10, Paragraph 3: "Safety is an important consideration with biologic therapies and, as above there have been particular concerns about the safety of JAK inhibitors when used for other conditions"

Page 10, Paragraph 5: "Taking into consideration the above information on short-term benefits seen in the trials but concerns about long-term safety, especially for JAK inhibitors.."

Page 32, Paragraph 3: "In summary, for adults and adolescents with moderate-to-severe atopic dermatitis inadequately controlled with topical or systemic therapies, or for whom topical or systemic therapies are not tolerated or are medically inadvisable, we identified benefits from short-term trials of these four agents but concerns about long-term safety, especially for the JAK inhibitors"

Suggested Revision: Include the word "oral" preceding "JAK inhibitors" to read "oral JAK inhibitors" in all 3 abovementioned statements.

IV. Recommendation to revise statements based on current evidence

A. Recommend stating consistently that long-term data were not published at the time of this report

Evidence related to long-term data of ruxolitinib are currently under review at an upcoming Dermatology conference and as such remains embargoed. We therefore recommend ICER make the following edits for consistency:

• On page 10, "There is currently inadequate information on long-term safety of topical ruxolitinib"

Suggested Revision: Long-term safety data for topical ruxolitinib were unavailable at the time of this analysis.

• On page 33, and 34, last sentence: "*No long-term data was identified*" **Suggested Revision:** Long-term data were unavailable at the time of this report.



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• On page 37, "Side effects of ruxolitinib cream were similar to or better than placebo, though long-term safety remains uncertain."

Suggested Revision: Side effects of ruxolitinib cream were similar to or better than vehicle cream. Long-term safety outcomes were unavailable at the time of this report.

B. Safety concerns due to systemic absorption of ruxolitinib cream

Recent publication by Gong X et al, have concluded that plasma ruxolitinib concentrations after treatment with topical ruxolitinib cream in patients in the 3 clinical trials are not expected to lead to systemic plasma concentrations associated with adverse effects commonly associated with oral JAK inhibitors.¹

• On page 10, the ICER draft evidence report states: "As a topical JAK inhibitor therapy, safety concerns are likely not as great as with oral JAK inhibitors, but there still is systemic absorption of the topical agent."

Suggested Revision: "Pharmacokinetic study was conducted using data from the phase 3 and phase 2 trials of patients with ruxolitinib cream 0.15%, 0.5%, 1.5% once daily and 0.75% and 1.5% twice daily. Plasma ruxolitinib concentrations after treatment with topical ruxolitinib cream in patients with up to 20% BSA affected by AD are not expected to lead to systemic plasma concentrations that may be associated with adverse effects commonly associated with oral JAK inhibitors."

• On page 35, first sentence under Uncertainty and Controversies: "Although ruxolitinib cream is a topical JAK inhibitor and concern for side effects may be lower, systemic absorption still occurs and..."

Suggested Revision: "Ruxolitinib cream, a JAK inhibitor, was specifically designed and formulated for topical application to minimize systemic absorption. Pharmacokinetic data for ruxolitinib cream suggest that adverse events associated with systemic absorption commonly associated with oral JAK inhibitors is not expected." (Gong X et al)

C. Statements related to sub-group analyses

Incyte disagrees with ICER's subjective conclusions made when assessing evidence from subgroup analyses. Subgroup analyses were conducted post-hoc and not prespecified or powered to show comparative evidence among them. We therefore

¹ Gong X et al. Pharmacokinetics of Ruxolitinib in Patients with Atopic Dermatitis Treated With Ruxolitinib Cream: Data from Phase II and III Studies. American Journal of Clinical Dermatology May 2021; https://doi.org/10.1007/s40257-021-00610-x



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recommend the following changes:

• Page 35, Disease Severity: "Subgroup analyses based on disease severity at baseline suggest qualitative better outcomes in patients with moderate disease compared to those with mild disease (see Evidence Tables D3.63-66)."

Suggested Revision: "Proportion of patients achieving IGA-treatment success in the sub-groups of mild and moderate disease severity were consistent with the overall study (see Evidence Tables D3.63)

• Page 35, Last Sentence: "The effectiveness of ruxolitinib in patients with darker skin complexions may be somewhat less, supporting the need for trials in broader populations."

Suggested Revision: "Ruxolitinib cream has demonstrated effectiveness in darker skin population, a population that is often under evaluated in clinical trial studies."

V. Comparative clinical assessment rating of ruxolitinib cream

Incyte respectfully disagrees with ICER's comparative net health benefit rating of C++ (comparable or better) based on the published evidence of ruxolitinib cream. We consider the evidence of ruxolitinib cream compared to topical emollients to be superior and recommend a rating of A based on the rationale below:

- Comparator and Treatment History: Patients in the 0.75% and 1.5% active arms in the Phase 3 clinical trials were compared to patients randomized to vehicle cream, which is a bland emollient. Other emollients such as Eucerin® cream were allowed during the double-blind period. Moreover, approximately 90% of all patients enrolled in the trials had a history of previous AD medication use, which included topical corticosteroids, calcineurine inhibitors or systemic therapy. Ruxolitinib cream demonstrated a high level of efficacy and was well tolerated in patients with AD regardless of previous use of topical or systemic therapy.²
- Strength of Evidence: Compared to vehicle, ruxolitinib cream 0.75% and 1.5% met key primary (proportion of participant achieving IGA-TS) and secondary endpoints (proportion of participants achieving EASI75, ≥4-point improvement in Itch NRS, clinically meaningful improvement in PROMIS Short Form-Sleep Disturbance, and Sleep-related impairment) at week 8. Additionally, a clear separation for both active treatment groups from the vehicle cream treatment

² Blauvelt et al American Academy of Dermatology, April 23-25, 2021: poster 27482





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group was evident at the very first post-baseline assessment (week 2). Antipruritic effect of ruxolitinib cream 0.75% and 1.5% cream assessed using Itch NRS score was evident as early as 12 hours after the first application. Furthermore, ruxolitinib cream has shown significant improvements in other well accepted and important efficacy and patient reported outcomes measures such as SOCRAD, DLQI,/CDLQI, POEM and WPAI.

Based on the totality of evidence, we ask ICER to revise their statements on pages 10 and 26 to the following: "...the evidence on ruxolitinib cream compared to topical emollients to be superior (A) with high certainty of a substantial (moderate-large) net health benefit."

We appreciate the opportunity to provide input on the draft evidence report and look forward to engaging with ICER and participating in the public meeting on July 23, 2021. All future correspondence continue to be directed to Vijay Joish at vjoish@incyte.com.

Sincerely,

Ahmad B. Naim, MD Vice President, US Medical Affairs Incyte Corporation Vijay N. Joish, Ph.D. Senior Director, HEOR, US Medical Affairs Incyte Corporation





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- 2. Blauvelt et al. Efficacy of Ruxolitinib Cream among Patients with Atopic Dermatitis Based on Previous Medication History: Pooled Results From Two Phase 3 Studies. American Academy of Dermatology Virtual Meeting Experience, April 23-25, 2021: poster 27482





June 11, 2021

Steven D. Pearson, MD, MSc, FRCP President, Institute for Clinical and Economic Review (ICER) Two Liberty Square, 9th Floor Boston, MA 02109

Submitted Electronically via: publiccomments@icer-review.org

Comments on ICER's Atopic Dermatitis Review Draft Report

Dear Dr. Pearson:

LEO Pharma Inc. ("LEO" or "we") appreciates the opportunity to provide comments on ICER's draft report for the review entitled "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis Effectiveness and Value". As a medical dermatology company, LEO is committed to ensuring patients have access to innovative treatments for atopic dermatitis. LEO respectfully offers the following points for consideration by ICER regarding the scope of this base case analysis plan.

Base Case Model Time Horizon

Atopic dermatitis ("AD") is a lifetime condition for some patients. In our clinical trials, patients suffered from moderate-to-severe AD for a median duration of 27 years prior to entry into those trials. The current 5 year base case model time horizon does not adequately capture the nature of the disease, nor the long-term value and potential risks of novel treatments for patients with AD. As such, we strongly recommend that ICER consider a 70 year lifetime horizon for the base case as was done in the 2017 AD review, rather than as a scenario analysis.

Investigational Tralokinumab's Q4W Dosing After 16 Weeks

We would also like to note that basing a 5 year model time horizon period solely on 16-week data does not consider the Q4W dosing option for investigational tralokinumab after 16 weeks. Q4W dosing was available to patients who achieved EASI 75 and/or clear or almost skin after 16 weeks of treatment in all three pivotal trials (ECZTRA 1, ECZTRA 2, ECZTRA 3). ICER has acknowledged within its report that dosing and utilization will impact model outcomes, and that inclusion of the option for tralokinumab every four weeks would lower treatment costs. We feel strongly that ICER should conduct a scenario analysis reflecting the Q4W dosing option. Additionally, voting question 13 cannot be adequately assessed if there is not an analysis of the Q4W dosing option included in the report.

Long-term safety data

ICER noted the need for long-term safety and efficacy data in the evaluation as noted on page 9 of the report:

1

¹ JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis Effectiveness and Value, pg.51.



"Safety is an important consideration with biologic therapies and, as above there have been Dermatology particular concerns about the safety of JAK inhibitors when used for other conditions. Additionally, though, tralokinumab is a novel inhibitor of IL-13 and we have limited long-term safety data."

It is critical to note that tralokinumab is a fully human monoclonal antibody with a different mechanism of action from the JAK inhibitors. In the report, ICER states the following about JAK inhibitors: "Though abrocitinib, baricitinib, tralokinumab, and upadacitinib appeared to have few serious harms reported from the trials of atopic dermatitis, oral JAK inhibitors approved for other indications, including baricitinib and upadacitinib, have label warnings about potentially causing serious infections, blood vessel disorders, cancer and death, and serious harms are more common at the higher doses studied. Whether certain oral JAK inhibitors or their use in patients with atopic dermatitis is associated with fewer long-term harms remains uncertain." Despite acknowledging that "no similar risks have been reported for tralokinumab," (pg. 32) the Draft Evidence Report subsequently classifies tralokinumab alongside the JAK inhibitors as having a "small (but nonzero) likelihood of a negative net health benefit" (pg.32). This equivalence of safety concerns is not merited by quantitative analysis and contradicts qualitative statements made elsewhere in the report.

Regarding longer term data, LEO would like to make ICER aware of key late-breaking clinical data that addresses this need for data on the clinical effectiveness and safety of investigational tralokinumab presented at the 2021 American Academy of Dermatology (AAD) virtual annual meeting. ECZTEND² is a 5 year, open label extension trial including subjects from 9 parent trials evaluating the safety and efficacy of tralokinumab. The interim analysis (n=1174 total) included data from 1 year (n=612) and 2 year (n=345) cohorts from 4 parent trials (ECZTRA 1-3 and 5). This ECZTEND interim analysis demonstrated that the long-term use of tralokinumab 300 mg Q2W was well tolerated and the overall safety profile was consistent with the parent trials, with no new safety signals observed.

Network Meta-Analysis Considerations

Trial design differences in AD clinical trials make it challenging to compare trials via typical indirect comparison methodologies. Key differences amongst trials may pose challenges when seeking to compare outcomes, particularly when these differences may impact active treatment and placebo differently. As such, indirect treatment comparison using network meta-analyses conducted from trials with differing methodologies should be interpreted with caution. Given the information shared by ICER, LEO has been unable to fully evaluate the methods used in the NMA.

In summary, we would like to reiterate our appreciation for the opportunity to provide public comments and your consideration of our recommendations.

Sincerely,

Andrine Swensen MS, PhD Senior Director, US HEOR on behalf of LEO Pharma

² Blauvelt A, et al. Long-term Improvements Observed in Tralokinumab-treated Patients with Moderate-to-severe Atopic Dermatitis: An ECZTEND Interim Analysis. American Academy of Dermatology Association Virtual Meeting Experience (AAD VMX); April 23-25, 2021. On-demand video oral presentation 29393.



Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285 U.S.A. www.lilly.com

June 11, 2021

Lilly Public Comment to ICER's Draft Evidence Report – Atopic Dermatitis

Eli Lilly and Company appreciates the opportunity to provide input on the Draft Evidence Report for ICER's assessment of Atopic Dermatitis (AD). We have outlined several important considerations, as well as some references to support these considerations within this assessment.

Comparative Clinical Effectiveness:

Study Inclusion and Dosing Information:

The BREEZE-AD1, BREEZE-AD2, and BREEZE-AD7 clinical trials studying baricitinib in patients with atopic dermatitis include only patients outside of North America and are not representative of a US patient population with moderate to severe atopic dermatitis.¹⁻³ BREEZE-AD5 is a North American study that best represents the US population.⁴ Lilly applauds ICER for highlighting that the 4 mg dose of baricitinib will not be available in the US. Lilly submitted data on the lowest efficacious dose of baricitinib in atopic dermatitis to the FDA at 2 mg.¹⁻⁴ Of equal importance, baricitinib 1 mg was studied in clinical trials per regulatory guidance, and this dose will be intended for patients with renal impairment who are unable to take the baricitinib 2 mg dose should baricitinib be approved for the treatment atopic dermatitis. This would be consistent with the current labeling for Olumiant in Rheumatoid Arthritis.⁵

Lilly Recommendations:

- ICER should provide detail on the geographic locations of clinical trials in their reports to allow readers to understand and interpret the patient populations assessed in each clinical trial. Specifically, inclusion of this detail in Table 3.1 or in Table D3.2 is preferred.
- ICER should evaluate only FDA-approved doses for the interventions identified within the final assessment.
- ICER should state that the 1 mg dose of baricitinib will be intended for patients with renal impairment who are unable to take the baricitinib 2 mg dose consistent with the labeling for Olumiant in Rheumatoid Arthritis in Section 3.2.

Outcomes:

BREEZE-AD1, BREEZE-AD2, BREEZE-AD5 all investigated patient reported outcome (PRO) measures that are important symptoms of Atopic Dermatitis and important aspects of the impact of Atopic Dermatitis on patients. Key PRO measures in the trials included but were not limited to the following: itch severity (Itch Numeric Rating Scale (NRS)), skin pain for example discomfort or soreness (Skin Pain NRS), night-time awakenings due to itch (Atopic Dermatitis

Sleep Scale item 2 (ADSS-2)), quality of life (DLQI, WPAI), anxiety and depression (HADS-Anxiety, HADS-Depression). Data can be found in publications, clinicaltrials.gov, as well as in data submitted to ICER during the data request period earlier this year.^{2-4,6-8} For quick reference, Lilly has provided a summary of the publicly available relevant data in Appendix 1 to this Public Comment.

Lilly Recommendations:

- ICER should recognize additional outcomes data important to patients in the discussion of baricitinib clinical effectiveness in Section 3.2 including itch (Itch NRS), night-time awakenings due to itch (ADSS-2), skin pain (Skin Pain NRS), work productivity (WPAI), and anxiety and depression (HADS-Anxiety, HADS-Depression). ^{2-4,6-8} ICER should reach out to Lilly if they have difficulty identifying this information in the submissions provided and referenced in this document in Appendix 1.
- ICER should at a minimum include the impact of baricitinib 2 mg on all PRO measures (e.g., itch, night-time awakenings due to itch, skin pain) as a part of the Potential Other Benefits section of the assessment as these endpoints are important to patients and help to inform prescribing behavior.

Subgroup Analyses and Heterogeneity:

On page 28 in the Disease Severity section, ICER states that baricitinib has qualitatively better outcomes in patients with severe disease compared to those with moderate disease. Lilly's data submissions support baricitinib efficacy in both moderate and severe patients, however, based on analyses of both IGA3 vs. IGA4, and body surface area involvement, the efficacy is qualitatively better in patients with moderate disease. Body surface area (BSA) is a tool utilized in dermatologic disease states to quickly and easily assess the extent of disease in clinical practice. In light of the clinical utility of BSA, it would be valuable to evaluate the baricitinib 2 mg data within this subgroup. The mean affected BSA at baseline in our studies ranged from ~40% to ~50%. Post-hoc analyses showed that ~90% of the EASI75 responders, and ~95% of patients achieving a score of 0 or 1 (clear or almost clear) with the validated Investigator Global Assessment for AD (vIGA-ADTM) scale, had a baseline BSA between 10-50%. Patients who responded to baricitinib 2 mg showed a clinically meaningful improvement in skin inflammation (50% improvement from baseline in affected BSA) and itch (at least a 3-point or greater improvement in the itch NRS) by week 4 and 8, allowing for early medical decision on whether patients should continue on baricitinib 2 mg therapy or not. 10,11

Lilly Recommendations:

- ICER should revise their statement about baricitinib efficacy to state that while baricitinib is effective in both moderate and severe patients with atopic dermatitis, it has qualitatively better outcomes in patients with moderate disease compared with severe disease on page 28 of the report.
- Due to the clinical utility of measuring BSA involvement in dermatology practice, ICER should include the baricitinib 2 mg impact on patients with BSA involvement of 10-50% within their Potential Other Benefits or Contextual Considerations section.

Network Meta-Analysis (NMA):

Lilly encourages ICER to honor its commitment to model transparency by providing additional detail on the NMA model parameters in their next release of the Evidence Report for Atopic Dermatitis. Specifically, Lilly would like to understand NMA model parameters such as the details of priors put on the estimates, including the between study standard deviation (SD). The NICE technical supporting documents (TSD) that are referenced within the NMA section recommend that the baseline is fitted independently. It is not clear in the methods section of the report if these models fit the baseline independently or simultaneously. In addition, Lilly would like to understand the between study SD, the deviance information criterion (DIC) and residual deviance for each model.

Since the models are adjusted for baseline risk, Lilly would like to understand the regression coefficient for baseline risk. By adjusting for baseline risk, the model favors treatments with higher placebo response and penalizes treatments where the placebo response is low. Placebo response rates are multifactorial, and while baseline risk adjustment can be used to account for some heterogeneity in trial design, it may not account for this effect sufficiently and can potentially introduce bias. It is therefore important that the report demonstrate the reasons for adjusting for baseline risk. The NICE TSD recommends looking at several different criteria to determine if adjusting for baseline risk is necessary. Lilly encourages ICER to include the following information in the Evidence Report to justify the use of the model adjusting for baseline risk:

- 1. Establishing whether the regression coefficient was significant by showing that the 95% credible interval (CrI) excludes 0.
- 2. Establishing whether the between-study standard deviation parameter (and its 95% CrI) was reduced in magnitude when adjusting for baseline risk
- 3. Establishing whether the DIC and the posterior residual deviance are improved when comparing with the unadjusted model
- 4. Plotting of the relative risk by placebo response

Lilly believes that a multinomial model is more appropriate for fitting EASI response scores as the scores are categorical. Rather than fitting three separate binary models, a probit model is more appropriate. Should ICER choose to convert to this type of model, Lilly asks ICER to include details of this type of model in their methods section in the primary report or in the appendices.

Finally, ICER's base-case NMA appropriately includes monotherapy clinical trials with placebo only as a common comparator. However, in a model sensitivity analysis, ICER conducted an NMA including the combination studies with the monotherapy studies in the section "Combined Placebo-controlled monotherapy and combination Trials in Adults (short-term)". There is not a common comparator linking these studies making it inappropriate to pool these studies. Further, in ICER's scoping document and research protocol, it lists the interventions of interest as monotherapies. The BREEZE-AD7 clinical trial, as well as Guttman-Yassky phase 2 clinical trial, are trials of baricitinib in combination with topical corticosteroids compared to placebo plus topical corticosteroids. Therefore, the trials of the interventions in combination with topical agents compared to placebo in combination with topical agents are out of scope for this assessment and for the NMA.

Lilly Recommendations:

- 1. ICER should provide additional detail on model parameters including the details of whether the baseline is fitted independently or simultaneously, the priors put on estimates, the between study SD, the DIC, and the residual deviance for each model.
- 2. ICER should include detail on the rationale and parameters to justify the use of a model that adjusts for baseline risk. In addition, ICER should highlight the heterogeneity of key trial criteria that justify the use of this type of model in the Contextual Considerations section of the assessment.
- 3. ICER should include details of the multinomial model structure in the methods section of the assessment.
- 4. ICER should keep the base-case NMA using placebo-controlled trials only, and not include the sensitivity analysis NMA with placebo plus topical agents as a comparator to keep consistent with the scope and because there is not a common comparator.

Comparative Value Analysis:

Utility Values:

Lilly is aligned with ICER's approach to use a pooled utility estimate across therapies to give the most robust understanding of the utility of achieving a clinical response for defined health states based on EASI scores. In Table 4.4, the BREEZE-AD clinical trials for baricitinib are not included in the pooled utility estimate. Because the BREEZE-AD5 utility response rates represent a North American population of atopic dermatitis patients, these utility values would be the most representative of the US patient utility for achieving a clinical response in atopic dermatitis and could be applied across all interventions included in the assessment or pooled with the estimates from other intervention trials. Further, additional clarity is needed on the estimates used in this assessment. It is not clear whether separate utility values are used for the moderate vs. severe health states.

Lilly Recommendations:

- If possible, ICER should provide the weighted averages of the utility estimates (means, standard deviations) without divulging the product or trial specific utilities that were submitted in confidence.
- ICER should clarify whether different utility values are used for moderate vs. severe health states.
- ICER should include the BREEZE-AD clinical trials, or specifically the BREEZE-AD5 clinical trial given its representation of US patients, in their determination of pooled utility estimates.
- ICER should be as transparent as possible in the inputs and assumptions included in this assessment.

Access and Reimbursement Considerations:

We continue to urge ICER to consider clinical, economic, and patient access implications of rebates used to negotiate formulary access in the autoimmune therapeutic class, including with respect to AD. Rebates are rarely equal for all available treatment options and negotiations can create barriers to more cost-effective therapies due to exclusions and step edits. In the

autoimmune market this dynamic is known as the "rebate wall," which is an issue that has received significant attention from Congress, the FTC, and ICER itself. 15-22 Further, we encourage ICER to consider the impact of rebate walls as it examines the implications of tiering, step therapy requirements and prior authorization criteria, in its forthcoming "Barriers to Fair Access Assessment" as rebate walls can drive utilization management techniques and formulary decisions. 22

Lilly Recommendation:

• ICER should encourage discussion of the implications of using rebates to negotiate formulary access during the forthcoming Roundtable Discussion and should acknowledge these potential implications in the Final Evidence Report for Atopic Dermatitis.

Sincerely,

Christian Nguyen, Pharm.D./MBA/MS

Vice President, Global Patient Outcomes & Real World Evidence

Eli Lilly and Company

Email: nguyen_christian_t@lilly.com

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Appendix 1.

	BREEZE AD56		BREEZE AD17		BREEZE AD28	
	2mg	Placebo	2mg	Placebo	2mg	Placebo
Itch NRS (≥ 4-point change)	25.2%	5.7%	12.0%	7.2%	15.1%	4.7%
Skin Pain NRS (change from baseline, LSM	-2.40	-1.03	-1.58	-0.84	-2.61	-0.86
(SE))	(0.27)	(0.34)	(0.29)	(0.24)	(0.30)	(0.26)
Night-time awakenings due to itch, ADSS-2	-0.99	-0.40	-1.04	-0.84	-1.21	-0.80
(change from baseline, LSM (SE))	(0.17)	(0.21)	(0.17)	(0.15)	(0.12)	(0.09)
HADS-Anxiety (change from baseline,	-2.55	-2.03	-1.83	-0.90	-1.92	-0.99
LSM (SE))	(0.32)	(0.44)	(0.33)	(0.28)	(0.38)	(0.33)
HADS-Depression (change from baseline,	-1.73	-1.31	-1.40	-0.37	-0.99	-0.28
LSM (SE))	(0.26)	(0.36)	(0.32)	(0.27)	(0.37)	(0.32)
WPAI- Absenteeism (change from baseline	2.34	3.41	-0.84	-0.49	-3.39	-4.40
LSM(SE))	(3.08)	(4.74)	(2.23)	(1.68)	(3.68)	(3.45)
WPAI- Presenteeism (change from baseline,	-19.33	-3.44	-11.53	-2.89	-19.71	-6.15
LSM (SE))	(2.99)	(4.04)	(3.44)	(2.60)	(3.90)	(3.87)
WPAI- Work Productivity Loss (change	-17.15	-0.88	-9.06	-2.57	-16.63	-7.15
from baseline, LSM (SE))	(3.52)	(4.85)	(3.83)	(2.89)	(4.65)	(4.65)
WPAI- Activity Impairment (change from	-22.53	-9.24	-10.80	-5.67	-23.25	-8.94
baseline, LSM (SE))	(2.40)	(3.33)	(2.57)	(2.16)	(3.12)	(2.74)

LSM = least square mean; SE = standard error. All data points provided are at week 16.



June 11, 2021

Steven D. Pearson, MD, MSc President, Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson:

Thank you for the opportunity to be included as a Key Stakeholder Organization for the 2021 evaluation of JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis (AD).

As the largest patient advocacy organization in the U.S. dedicated solely to all forms of eczema, we have appreciated the intention for this review to acknowledge and incorporate important aspects of the clinical and quality of life lived experience for the over 31 million individuals and families affected by AD.¹⁻³ Our organization, with the support of other key AD patient advocacy organizations, provided feedback and questions through each stage of the value assessment process, and NEA additionally appreciated the opportunity to meet with the modeling team to reiterate areas of importance. Given this, while we note that certain aspects of our feedback have been considered, several previous points from our comment letters have not been fully addressed in the draft report, providing future opportunities to increase the patient-centricity of the final report or future value assessments (Table 1).

Table 1: Areas of opportunity to increase the patient-centricity of atopic dermatitis treatment value assessment.

Comment	Opportunity
Cost-consequence analysis for depression/anxiety	During our call with the modeling team and in our April 2021 comment letter we articulated the importance of anxiety/depression outcomes from the patient perspective. In the current health state model structure, patients either remain in a non-responder state or transition to one of three responder states. We commend the inclusion of itch and sleep into the cost consequence analysis, as these are outcomes of importance to patients. However, given the significant mental health burden of AD, which often correlates with uncontrolled disease ⁴⁻⁶ , existing literature could have been used to additionally estimate the potential benefits of reduced anxiety/depression across the therapies in the responder states.

Comment	Opportunity
Pediatric/adolescent scenario analysis and separate voting questions	Based on our call with the modeling team we anticipated ICER would consider adding a pediatric-focused scenario analysis, as completed and ongoing clinical trials for abrocitinib, upadacitinib and tralokinumab have included ages 12 and up, as well as the potential for off-label usage. While omitted for the current report, we suggest this remains an opportunity for the final report or for more specific discussion prior to the final vote. Clinical benefits in the pediatric population may provide greater value when considering the potential spillover benefits to their adult caregivers. ⁷⁻⁹
Consideration of out-of-pocket costs	While the "average" eczema patient experiences substantial financial difficulties due to the well documented economic burden of this disease ¹⁰ , patients of lower socioeconomic status are particularly vulnerable. Without explicit consideration for health plan policies that may place certain AD therapies on tiers with higher out-of-pocket cost-sharing, lower socioeconomic status patients could be impacted more than those with more expendable income. Knowing this information, different scenarios could be modeled to account for costs and benefits differences impacted by changes in out-of-pocket expectations.
Highlight the revisions made through each validation step	In the draft report, model validation was described on page 51 that includes steps the research team took to refine the model and data used. It would add clarity for the audience to highlight which revisions were made based on patient group or other stakeholder feedback. This would acknowledge the input and engagement of external stakeholders as well as improve the transparency of the validation steps and general value assessment process.
Add a column for modified societal perspective costs from table E4.2 to Table 4.9	Rather than separating the modified societal costs, we recommend following best practices and including societal costs results alongside the base case costs in the main results table.
Section 4: "Long-Term Cost Effectiveness" – Inappropriate for a 5-year base case analysis	The incremental cost-effectiveness analysis for the base case focuses on a 5-year time horizon. Using the phrase "Long-Term" in the title of this section implies a lifetime analysis typically chosen by economists looking to capture the more complete picture. Reviewers should be reminded this is a truncated analysis. ICER should remain consistent in its use of "short-term" and "long-term" as it does on page 8 of the ICER Value Framework methods document describing the rationale

of a "short-term" 5-year time horizon typically chosen in its budget impact analysis.

We would like to recognize the hard work of the ICER team in synthesizing the evidence and estimating the value of JAK inhibitors and monoclonal antibodies for the treatment of AD. We understand the limits created by the value framework with a pre-specified focus on the value to the health system (or health system perspective) rather than the patient or society. The report acknowledges the significant burden AD places on "all aspects of patients' lives and those of their family and caregivers" in the first paragraph of the Executive Summary. We appreciate that ICER recognizes these burdens. While the current draft report falls short in addressing or incorporating the full range of clinical and economic burdens of AD in the value assessment, we hope to continue working with your team to provide additional context for the final report and for future evaluations that impact the AD patient community.

Specifically, through this process we recognized that out-of-pocket costs, patient affordability, and access are not currently incorporated into the value assessment in a meaningful way. Through our patient engagement activities, we have identified significant health disparities in AD that may have an impact on different components of care. While ICER may not be responsible for the ultimate access decision or formulary determination, recognizing the potential consequences (intended and unintended) on formulary design and access may be an area of opportunity for future evaluations. Lower socioeconomic patients are often the most significantly impacted by more restrictive managed care mechanisms, so special considerations may need to be made to address these populations.

Lastly, we offer a few specific comments on the draft voting questions for the committee for your consideration to help during the deliberation of the New England CEPAC (Table 2).

Table 2: Considerations for committee voting questions.

Topic Area	Consideration
Contextual Considerations Questions	"Acuity of need" – We read acuity to imply a
Section (Q6):	serious AD crisis leading to urgent/emergency care
	and/or hospitalization. Please clarify this
	terminology if ICER means to focus on whether the
	patient has severe AD, or other intended focus.
Contextual Considerations Questions	Please clarify what may be included in the "Other"
Section (Q8)	category during voting.
"Long-term Value for Money" Section:	It may be confusing using the phrase "long-term
Questions 15 & 16	value for money" for baracitinib and upadacitinib on
	question 15 and 16 when the base case incremental
	cost-effectiveness analysis focuses on 5 years. The
	long-term analysis was only included as a scenario
	analysis and if the committee focuses on Table E4.4,
	they might see a very different answer.

ICER Review of AD Treatments: Feedback on Draft Evidence Review & Voting Questions June 11, 2021

4

We hope that these comments are helpful as you finalize the evidence report and voting questions, and we again thank you for willingness to engage with our organization and our patient community.

Sincerely,

Julie Block

NEA President and CEO

Lawrence F Eichenfield, MD

Le Eche field

Chair, NEA Scientific & Medical Advisory Council

With Support From:

Kenneth Mendez President and CEO

Asthma and Allergy Foundation of America

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June 11, 2021

Steven D. Pearson, MD, MSc, FRCP President, Institute for Clinical and Economic Review One State Street, Suite 1050 Boston, MA 02109 USA

RE: Draft Evidence Report "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"

Dear Dr. Pearson:

Patients Rising Now advocates for patients with serious and chronic conditions to have access to life-improving and life-saving therapies and services. Access to such treatments and services is essential, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, clinicians, media, health policy experts, payers, providers, and others to foster people-centered discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care innovations and advancements in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER's May 14th Draft Evidence Report, "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis." Our comments about the draft report are organized below into sections about People-Centered Perspectives; Data, Modeling, Assumptions and Uncertainties; and Additional Points.

<u>People-Centered Perspectives</u>

Atopic dermatitis – commonly known as eczema – is a complex immune disorder affecting the skin. The draft report does a reasonably good job of describing many of the clinical and personal challenges faced by people with atopic dermatitis. But it is also clear that better treatments for atopic dermatitis are needed because of great variability in how the condition affects individuals and people who have various co-morbidities. As the draft report states:

- "Despite available treatments, many individuals do not respond to multiple different topical and systemic therapies supporting the need for new treatment options."
- "There was broad recognition that current therapies do not address all of the needs of patients with atopic dermatitis."

Better treatments are needed not just to improve clinical outcomes, but perhaps more important, to improve patients' productivity and quality of life. As described in the draft report: "For students it can affect school attendance and lead to distraction when in class, negatively impacting developmental milestones. Similarly, atopic dermatitis can affect work through missed days, decreased work performance (presenteeism), missed promotions, limited career options, and even disability from one's chosen profession. The net result is a financial impact on individuals and families over the course of one's life in terms of educational and work advancement opportunities delayed or lost." Unfortunately, that reality is minimally recognized in the draft report's analyses and conclusions.

There are similar important aspects of how atopic dermatitis affects people and their treatment choices that the draft report fails to acknowledge or incorporate into its analysis and conclusions.

First, a key data point cited in the draft report highlights the personal financial toll of atopic dermatitis: "The overall costs associated with atopic dermatitis are estimated to be \$5.3 billion in the US, including over \$1 billion in health care costs." This means that the personal (i.e., non-health care costs) are about 400% greater than the health care costs. This four-to-one ratio quantifies the serious limitations of the draft report, its analyses, and its conclusions since it focuses almost exclusively on the costs that are less than 20% of the actual impact of the disease.

Second, although the draft report discusses how atopic dermatitis significantly impairs an individual's work and life activities, it fails to capture the full consequences of the "social embarrassment and isolation" resulting from a person's skin appearance, and how that leads to "psychological distress including loss of self-esteem, anxiety, depression, and suicidal ideation." Specifically, the draft report does not explore research about atopic dermatitis leading to greater suicide attempts (although it is unclear if the condition causes an increase in deaths from suicide) or other mental, emotional, or behavioral health issues.

Third, while the draft report – like much of ICER's work – focuses on a small group of treatments, for people with atopic dermatitis and their clinicians, the actual range of treatment options is much wider and more complex. This discrepancy is apparent when comparing the draft report's scope with that of the two actual systemic reviews and technology assessments summarized and referenced in Section D5 of the Supplemental Material. Viii One of those reviews evaluated "20 different medications," and the other "13 different approved treatments in Europe," in contrast with only six treatments included in the draft report. For clinicians, patients, policy makers, and others concerned with improving the quality and efficiency of health care within the populations of their purview (e.g., the management of Medicare, state Medicaid programs, private health insurance, Veterans Affairs' health care, Department of Defense health care, or the Indian Health Service), the question is not about evaluating small subsets of treatment options, but rather how to develop and implement appropriate policies for ensuring quality and efficient health care for the population for whom they are either paying for their health care or actually delivering their health care services and treatments. In contrast – as we've noted before – ICER's work is illusionary in that it assumes a unified, single health care system, and it assumes that there is a single health care budget for that "system."

And lastly, in the subgroup analysis, the only differentiators are age and disease severity. However, there are some indications that women and Black Americans are more likely to have severe atopic dermatitis. Even though the available data may be limited or not definitive, given the inherent underrepresentation of women and people of color in clinical trials, and the disparities and inequities they continue to experience in access to health care in the U.S., we strongly believe that the draft report should at least address the important issues for those subgroups, namely potential issues related to the need for new treatments, and challenges accessing them. And in this area, we note that the draft report states, "Given the large impact of atopic dermatitis in African-Americans and the importance of skin appearance on outcomes of treatment more broadly, few trials included a sizable number of patients with darker skin complexions, and we are not aware of any trial that has reported outcomes among those with darker

skin complexion." So while ICER appears to be aware of this issue, we suggest that it be more explicitly stated in the draft report, and that the need for better and more extensive data collection on those subgroups, and greater inclusion of people of color in future research, be stressed by ICER.

Data, Modeling, Assumptions, and Uncertainties

Because the draft report does a deep numerical dive into the available research for six different medicines, it contains an extensive amount of data. However, just because there are numbers, and those numbers are compared and plugged into formulas for evaluative purposes, does not make the resulting "output" insightful, useful, or even correct. We are reminded of the old adage: "Not everything that counts can be counted, and not everything that can be counted counts." Breaking this down into its two parts, we see that the first part relates to the reality that patient concerns and perspectives are often hard to measure and are often not robustly evaluated in clinical research. For atopic dermatitis treatments, we are gratified that there are so many different patient-focused metrics as described in the draft report's Supplemental Materials Definition section. XII However, of those 11 different outcome measures, the draft report focuses on two that are investigator-measured (i.e., EASI and IGA), rather than patient-reported or primarily related to quality of life. This selection of measures may be because of the structure and compatibility of data across trials, but it underscores that the way data is collected and chosen for evaluation drives both thinking and conclusions.

To that point, we appreciate that uncertainties about metrics such as EASI are discussed in the draft report, e.g., "...we assumed that levels of EASI response are associated with differences in health-related quality of life." However, there may be differential effects of the treatments modeled on conditions such as itch and sleep that are not completely captured by generic quality of life instruments. However, available data did not support the use of treatment-specific utilities. Additionally, there may be incremental effects of some of these treatments on quality of life in sub-populations of people with atopic dermatitis, such as those with co-occurring asthma or chronic rhinosinusitis, which are not explicitly captured in the current model." Because of the importance of those uncertainties, they should have been explored in greater depth and earlier in the draft report, particularly since one researcher stated that the use of such measures "in clinical practice is not recommended," and that "both objective and subjective assessments of disease severity are important to assess, consideration of clinical characteristics such as disease recurrence or persistence, as well as location of the affected areas, should be considered in the overall judgement of disease severity and consideration of therapy choice."

And more generally concerning ICER's assessment approach, a recent review of books on the topic of evaluation metrics^{xv} produced the following insights and quotes that are very illuminating:

- "Seduced by their seeming precision and objectivity, we can feel betrayed when the numbers fail to capture the unruliness of reality."
- "As Tim Harford writes, data 'may be a pretty decent proxy for something that really matters,' but there's a critical gap between even the best proxies and the real thing—between what we're able to measure and what we actually care about."
- "To simplify the world enough that it can be captured with numbers means throwing away a lot of detail. The inevitable omissions can bias the data against certain groups."
- "Numbers are a poor substitute for the richness and color of the real world."

• "Numbers don't lie, except when they do." [emphasis added]

Another problematic assumption in the draft report is the relationship between atopic dermatitis and mortality. The draft report states, "We assumed that atopic dermatitis disease and treatment did not affect mortality," and one of the Long-Term Cost Effectiveness analysis' assumptions is "Atopic dermatitis disease and treatments do not affect mortality." However, research indicates higher rates of suicide attempts, and overall higher mortality, i.e., one analysis "found that patients with atopic eczema had an 8-14 percent increased risk of death due to infectious, digestive, and genitourinary causes. They noted that increased mortality risk was mainly in those with the most severe or more active atopic eczema. Patients with severe atopic eczema had 62 percent higher overall risk of death. These findings are consistent with previous studies." **xviii**

The draft report also primarily compared trial data that looked at monotherapy, but advancement and actual practice may include a combination of treatments, including systemic and topical. Once again ICER may be looking at the theoretical that does not reflect reality. As the report itself describes in discussing its modeling, "the NMA analyses that informed our effectiveness estimates in the model were derived from phase II and III RCTs that compared the treatments of interest to placebo with only the added use of topical emollients at 16 weeks. Therefore, the incremental value of these treatments may not be generalizable to patients using topical steroids and/or calcineurin inhibitors." xix

Overall, the extensive data, charts, graphs, and comparative analytics across six different treatment options contained in the document made the draft report very user unfriendly. In other words, for unsophisticated readers, the content is probably indecipherable, leaving those individuals to look at the conclusions and assume that ICER's internal and external teams got everything correct. And for sophisticated readers and analysts – such as those who decide clinical care, formulary placement or reimbursement policies – there remains the question about how the information in the draft report fits in with the much larger array of treatment options for atopic dermatitis (including possible combinations of treatments), or the much larger issue of managing access and coverage for immunomodulator medicines. On both points, the draft report clearly fails usability tests in multiple and different ways.

Additional Points

- Please explain how the New England CEPAC is both a "core program of ICER" and "an independent committee."xx
- The draft report states that "ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments," however, that is not true. Health Benefit Price Benchmarks were included in ICER's recent draft report about Alzheimer's treatments. And further as we pointed out in comments to that draft report ICER's draft reports should absolutely include benefits price benchmarks from a societal perspective, particularly in this draft report because (as noted above), there is a 4:1 ratio in societal to health care costs. To add to the draft report's inconsistencies in this area, the Long-term Cost Effectiveness Supplemental Information goes into some detail about analyzing the situation from a societal perspective, *xxii but here too the draft report ignores the evidence about increased mortality related to atopic

- dermatitis. This is another example of ICER making up its own arbitrary rules but only following them when it sees fit to do so.
- The draft report states that as part of building the comparative clinical effectiveness model the assumption was made "that background topical medication is not an important effect modifier." Does this mean that ICER believes that topical medications are ineffective? We would appreciate ICER specifically responding to this point and to the clinical logic behind that assumption as it relates to ICER's modeling in the draft report and hence the draft report's conclusions.
- There is no discussion about the biological mechanism of action of atopic dermatitis, aside from it being related to "problems with the body's immune system" or as an "allergic condition," while also noting that people with atopic dermatitis also commonly have allergies and asthma. Such general and imprecise language does a disservice to readers. According to Mt. Sinai Medical Center, atopic dermatitis is an autoimmune disease at the molecular level, xxvi and the Immune Deficiency Foundation also discusses atopic dermatitis within the spectrum of autoimmune skin diseases. xxvii The draft report should include more discussion about the underlying cause of atopic dermatitis, and if the draft report's writers and reviewers disagree with the conclusions noted above, then those disagreements should be explained.
- Given the extensive data density in the draft report, it is critical that the language be crisp, clear, and correct. However, there are several places in the draft report where words are missing, the meaning is unclear, or the text is complex and hard to decipher. Such poor writing (or faulty proofreading or copyediting) does a severe disservice to readers and ultimately to anyone who might use ICER's reports for anything substantive. For example:
 - o In this sentence, we believe the word "report" is missing: "Concerns about lack of long-term data for dupilumab, noted in ICER's 2017, have been alleviated over time based on published data and widespread use in clinical practice."xxviii
 - And this sentence is misleading: "Non-pharmacologic treatments are recommended to maintain and prevent flares." That is, we do not believe that treatments are recommended to maintain flares.
- In the draft report, the acronym AD is used to refer to Atopic Dermatitis, but it is not in the list of acronyms on page vii of the draft report nor could we find it specified in the text of the draft report. While that may seem obvious, in the previous draft report AD was used for Alzheimer's Disease, and that abbreviation was noted in on page viii of that draft report.

Conclusions

Patients Rising Now is pleased that people with atopic dermatitis have many treatment options. Like many complex health conditions that have very different presentations and courses for different people, and where there are multiple types of treatment options, individualization of care and close coordination with clinicians is important. Unfortunately, we see the draft report as thwarting that goal. Indeed, we are concerned (once again) that through ICER's myopic cost-fixated lens, the draft report will serve to reduce access and impair patient-clinician care planning and coordination.

Sincerely,

/Enn, M. Wilcon

Terry Wilcox

Co-Founder & Executive Director, Patients Rising Now

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Draft report, p. 12
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9 19#:~:text=The%20increase%20was%20higher%20in,gender%20did%20not%20influence%20prevalence

ii Draft report, p. 14

iii Draft report, pp. 13-14

^{iv} Draft report, p. viii

v Draft report, p. 11

vi Draft report, p. 13

vii "[P]atients with AD were 44% more likely to exhibit suicidal ideation (pooled odds ratio, 1.44; 95% CI, 1.25-1.65) and 36% more likely to attempt suicide (pooled odds ratio, 1.36; 95% CI, 1.09-1.70) compared with patients without AD. Studies investigating completed suicides in patients with AD had inconsistent results." https://pubmed.ncbi.nlm.nih.gov/30540348/

viii Draft report, p. 301

https://atopicdermatitis.net/eczema-statistics; https://nationaleczema.org/research/eczema-facts/, and https://link.springer.com/chapter/10.1007/978-3-319-72156-

^x Draft report, pp. 29-30

xi Often attributed to Albert Einstein, but more likely originating with William Bruce Cameron, https://quoteinvestigator.com/2010/05/26/everything-counts-einstein/

xii Draft report, pp. 70-72

xiii Draft report, p. 51

xiv "Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document. Section II: Tools for Assessing the Severity of Atopic Dermatitis," Gooderham et al., Journal of Cutaneous Medicine and Surgery, 2018, Vol 22(IS)10S-16S

^{xv} "What Data Can't Do: When it comes to people – and policy – numbers are both powerful and perilous," Hannah Fry, New Yorker, March 29, 2021, pp 70-73

xvi Draft report, p. 37

xvii Draft report, p. 40

xviii https://practicaldermatology.com/news/people-with-severe-atopic-dermatitis-may-have-increased-risk-of-death-from-several-causes

xix Draft report, p. 52

xx Draft report, p. iii

xxi https://icer.org/wp-content/uploads/2020/10/ICER ALZ Draft Evidence Report 050521.pdf

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4 June 2021

PUBLIC COMMENT FOR REVIEW OF ATOPIC DERMATITIS

I refer to your recently released Draft Evidence Report for Atopic Dermatitis (AD)¹.

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment fails to meet the standards of normal science ^{2 3}. That is, your reports lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of measurement theory in confusing ordinal scales with interval and ratio scales, and simple logic in driving claims by assertions and assumptions.

While you might view your standards and reports, and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. The QALY, for example, as you have been informed on a number of occasions, is a mathematically impossible construct with a paper in *F1000Research* and a letter to *Value in Health* pointing this out ^{4 5}. As noted in the latter, we have now experienced 30 wasted years in health technology assessment, with ICER perpetuating this charade. The key point is that in the case of new and emerging therapies for atopic dermatitis we have too little data to make even a reasoned, and scientifically valid, claim for pricing and budget impact. This should be put on hold until more data become available instead of rushing in to invent modelled claims.

Let me consider the assertion regarding your belief that the EQ-5D preference instrument has ratio properties. For a measure to have ratio properties there must be no possibility whatsoever that the instrument can generate negative values. The true zero is a universal reference for any measure that claims to have ratio properties. We might believe it if you could prove, not assert, that there is no possibility of a respondent to the symptoms and response levels of the instrument reporting negative values.

Clarification on your use of preference scores requires more information than has been provided in your draft evidence report. Unfortunately, we have no idea as to what these scores actually are for mild, moderate and severe stages of AD. They are blanked out. All we have is the Delphic utterance from the internationally respected CHOICE expert group at the University of Washington, College of Pharmacy that in constructing your imaginary assumption driven claims for the pricing and recommendations for atopic dermatitis therapies were 'weighted by a single set of health state utility values from pooled manufacturer data to derive quality-adjusted life-years (QALYs)'. Seeking further clarification on these utility scores the process is described by the University of Washington expert group as follows:

We derived health state utilities for the non-responder and responder states by pooling utility estimates from manufacturer submitted data. We estimated weighted average utility values for each health state, combining estimates from all treatments with data available by health state. We considered therapy-specific health state utility values to capture benefit beyond EASI score, however the available evidence did not support differential utility scores by treatment (p. 42).

No further details are given. This is unfortunate because if the protocols for the various AD trials are reviewed (Clinicaltrials.gov: ECZTRA 1&2; MEASURE UP 1 & 2; AD UP; and SOLO 1&2) there is no evidence from the list of secondary outcomes for each of these of any health related quality of life or just quality of life instrument that is designed to generate either direct or indirect preference scores. At best, we have the ordinal Dermatology Life Quality Index (DLQI) in two trials (ECZTRA 1 & 2 and SOLO 1 &2) which simply provides an aggregate of 10 4-level Likert scales (scores 0 - 30). Other than that I have no idea how the University of Washington Expert Group then proceeded to create utility values for a ratio scale with a true zero and a range of 0 = death to 1 = perfect health. I presume, as these are all secondary endpoints for the various protocols that they were all powered to create a 'composite' utility scale. Can you confirm? It might also be pointed out that if these various inputs from manufacturers are patient reported outcomes with ordinal properties, then the calculations vaguely described by the University of Washington expert group are mathematically impossible (with a further concern that they lumped together utilities from different instruments). Ordinal scales can only support nonparametric assessments. I am not sure if the Washington expert groups understands the need to conform to the axioms of fundamental measurement in statistical and econometric analysis (let alone building imaginary simulation models); if so, this is a major concern that ICER and the University of Washington should address. As a renowned university research group I would have thought their training would have included measurement theory (and some elementary logic to include Hume's Problem).

Given this, it might be pointed out that in your previous review and imaginary modelling for Dupilumab in moderate to severe AD you provide EQ-5D-3L utility values (source Sanofi data on file) ⁶. For patients with moderate disease (IGA), the utilities ranged from 0.684 (baseline) to EASI 50 0.892, EASI 75 0.895 and EASI 90) 0.907 while for severe disease (IGA4) the baseline was 0.536 to EASI 75 0.535, EASI 75 0.090 and EASI 90 0.911.

What I find puzzling is that there are a range of preference scores for AD available from the literature; perhaps your expert group did not think a systematic review worthwhile? These are well documented and include the impact of demographic factors as well as comorbidities typically associated with AD as well as systematic reviews. Of particular note is the recent study by Silverberg et al utilizing the *AD in America Survey* sampled from the long standing GfK knowledge panel (n=8,217) ⁷ Applying the SF-6D preference instrument yielded a mean AD

score of 0.69; mild AD 0.73 and moderate to severe AD of 0.63 As this is an ordinal scales these mean values for the SF-6D are actually incorrect; they should have reported medians or modes.

A study by Anderson et al utilizing the EQ-5D-5L and a visual analog scale (VAS), covering the US and selected European countries found for the US overall a EQ-5D-5L score of 0.77 for moderate AD and scores between 0.69 and 0.42 for severe AD ⁸. The VAS yielded, for the US, scores of 75.0 for mild AD, 67.8 for moderate AD and in the range 63.5 to 55.4 for severe AD (out of 100).

Returning to your belief that preference scales, such as the EQ-5D-5L, are in fact ratio scales in disguise with a true zero, it is worth noting that in the Andersen study 26 persons with AD were reported with negative EQ-5D-5L values ranging from -0.003 to -0.53 (Figure 1). Presumably these can be ignored in the belief held by the University of Washington expert group, that ordinal preference scores have undeniable ratio properties. Negative scores are merely inconvenient inconsistencies.

If your team at the University of Washington had probed a little further they would have encountered a patient centric need fulfillment quality of life instrument which meets the standards for fundamental measurement. This is the Quality of Life Index for Atopic Dermatitis (QoLIAD) first developed in 2004, it has been revised and used to create interval scores in AD trials including most recently Dupilumab in moderate to severe atopic dermatitis ⁹ ¹⁰.

As it stands, manufacturers in receipt of your recommendations for pricing and access for AD therapies should just reject them as irrelevant.

Yours sincerely

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June 11, 2021

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RE: Pfizer Comments on ICER's "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis" Draft Evidence Report

Dear Dr. Pearson and ICER AD Review Team,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis" Draft Evidence Report (DER).¹

We appreciate ICER's efforts to seek input from a broad range of stakeholders. Pfizer is committed to discovering medicines and vaccines that enhance the health of patients, their families, and society, with the ultimate goal of offering breakthroughs that will change patients' lives. In addition, we are dedicated to working with all stakeholders to identify solutions for creating a more effective, efficient, and equitable health care system for patients.

Based on our review of the DER, there are 6 areas we would like to address:

- 1. ICER's evidence rating for abrocitinib
- 2. Inappropriate speculation on treatment population
- 3. Presentation of the cost-consequence analysis
- 4. Discontinuation probabilities applied to emollients in the cost-effectiveness model
- 5. Data inconsistencies
- 6. Draft Voting Questions

1. Elevation of abrocitinib evidence rating when compared to dupilumab and emollients

On page 32 of the DER, ICER reports an evidence rating of "insufficient" (I) when comparing abrocitinib to dupilumab and an evidence rating of "promising but inconclusive" (P/I) when comparing abrocitinib to topical therapies alone. In the comparison of abrocitinib to dupilumab, ICER notes the "I" rating as "any situation in which the level of certainty in the evidence is low", whereas ICER states the "P/I" rating for abrocitinib compared to topical therapies alone as "demonstrating a moderate certainty of a small or substantial net health benefit, with a small (but nonzero) likelihood of a negative net health benefit."

We disagree with these evidence ratings and respectfully recommend that ICER elevate the evidence rating of abrocitinib compared to dupilumab to a "Incremental or Better/B+" rating, defined as "moderate certainty of a small or substantial net health benefit, with high certainty of

at least a small net health benefit." The rationale for this proposed change is based on the following evidence available in the literature:

- 1. In the JADE (JAK1 Atopic Dermatitis Efficacy and Safety) COMPARE phase 3 clinical trial (NCT03720470), abrocitinib was directly compared to dupilumab at week 2 with respect to itch response (PP-NRS4). Statistical superiority of 200 mg abrocitinib and numerically higher response of 100 mg abrocitinib was demonstrated for this endpoint.² In addition, a post-hoc analysis presented at the 2021 American Academy of Allergy Asthma & Immunology congress, showed that treatment with abrocitinib 200 mg provided numerically greater and more rapid responses than dupilumab across stringent efficacy endpoints (EASI-90, IGA-0, DLQI-0/1, etc.).³ Response rates relative to placebo in the abrocitinib 100 mg and dupilumab groups were similar.³
- 2. Furthermore, in a recently published network meta-analysis (NMA) of systemic therapies for moderate-to-severe AD which used fixed-effects and random-effects Bayesian NMA models, abrocitinib 200 mg once daily (QD) was shown to have higher rates of EASI response compared with dupilumab 300 mg every 2 weeks (Q2W) in both monotherapy and combination therapy networks. Specifically, in the monotherapy network, abrocitinib 200 mg QD was estimated to have a >97.5% probability of superiority over dupilumab 300 mg Q2W with respect to EASI-50, EASI-75, and EASI-90. In the combination therapy network, abrocitinib 200 mg QD had the highest observed EASI-50, EASI-75, and EASI-90 response rates and was estimated to have a 96% probability of superiority over dupilumab 300 mg Q2W. We believe these probabilities, which were based on all clinical evidence available at the time of this NMA's systematic literature review, would surpass the threshold for "high certainty of at least a small net health benefit" of abrocitinib over dupilumab, consistent with a "B+" rating.
- 3. In addition to clinician- and patient-reported outcome measures collected in randomized clinical trials, patient preference is an important consideration of net health benefit not traditionally captured in NMAs or economic models. A recently published study sought to quantify patient preferences for systemic AD treatment attributes and differentiate between systemic treatments using a discrete choice experiment. The results indicated that patients significantly preferred an oral daily administration over a biweekly injection and also preferred treatments with more rapid effect of itch relief. We believe both characteristics of abrocitinib should be considered as part of the net health benefit rating.

Similarly, we respectfully ask ICER to elevate the evidence rating of abrocitinib compared to topical therapies alone to a "B+" based on the following evidence available in the literature, whereby superiority to placebo was consistently shown:

1. Across the abrocitinib JADE monotherapy trials included in ICER's assessment (MONO-1⁶, MONO-2⁷, Phase 2b⁸), patients were permitted to use topical non-medicated emollients. Abrocitinib 200 mg and 100 mg consistently and significantly improved signs and symptoms of moderate-to-severe AD compared with placebo. Namely, more patients treated with abrocitinib achieved primary and key secondary IGA, EASI-75, and itch score responses compared with patients treated with placebo. In addition, when considering both commonly-used and higher threshold efficacy endpoints, a post-hoc pooled analysis of the adult cohort of these 3 monotherapy trials found that higher proportions of patients treated

with abrocitinib (200 mg, 100 mg) versus placebo achieved PP-NRS4 (47.1%, 34.7% vs 14.8%), EASI-75 (62.3%, 41.9% vs 12.2%), PP-NRS 0/1 (31.7%, 20.1% vs 4.8%), or EASI-90 to <EASI-100 (29.3%, 15.9% vs 5.9%) responses at week 12.9

2. Abrocitinib combination studies had similar patterns. In JADE COMPARE, all treatment groups were required to use emollients twice daily and therapy with a medicated topical (applied once daily) was started on day 1 of the treatment period. Both doses of abrocitinib demonstrated superiority compared to placebo when assessing IGA response at week 12 and 16 (p < 0.001), EASI 75 response at week 12 and 16 (p < 0.001), and itch response (PP-NRS) at week 2 (p < 0.001).

In the JADE TEEN trial in adolescents, abrocitinib QD (200 mg, 100 mg) was compared to placebo in combination with standardized medicated topical therapy and found that at week 12, more patients treated with abrocitinib (200 mg, 100 mg) versus placebo achieved IGA (46.2%, 41.6% vs 24.5%; p<0.05 for both), EASI-75 (72.0%, 68.5% vs 41.5%; p<0.01 for both), and PP-NRS4 (55.4%, 52.6% vs 29.8%; p<0.01 for 200 mg vs placebo) responses.¹⁰

- 3. Similarly, in the recently published NMA cited above, across both abrocitinib doses and monotherapy/combination studies, abrocitinib was estimated to have a 97.7%-100% probability of superiority over placebo/placebo + topical therapy with respect to IGA and PP-NRS response.⁴ We believe these probabilities exceed the threshold for "moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit" and the size of the efficacy differences between abrocitinib and placebo arms represents a "substantial" net health benefit, consistent with a "B+" rating.
- 4. In the 2017 evaluation of dupilumab for moderate-to-severe AD, ICER rated the clinical evidence for dupilumab relative to treatment with emollients with or without continued failed topical treatments a "B+" rating, despite a similar number of key trials (SOLO 1, SOLO 2, LIBERTY AD CHRONOS, Thaci 2016, and Blauvelt 2016) and follow-up length (16 weeks) as the available abrocitinib data package. Is Similarly, ICER identified 5 RCTs of abrocitinib varying in duration from 12 to 16 weeks of treatment comprising the evidence base of the current comparative clinical effectiveness assessment, all of which demonstrated superiority of abrocitinib compared to placebo on the primary endpoints.

Finally, a recently presented integrated safety analysis included 2856 patients in the all-abrocitinib cohort (pooled from 6 studies including a long-term extension study); 1248 had ≥24 weeks and 606 had ≥48 weeks of abrocitinib exposure. Results of this integrated safety analysis were consistent with results in individual trials. Based on this analysis, abrocitinib was well tolerated, with a safety profile appropriate for long-term treatment in this population.

2. Inappropriate speculation on treatment population

ICER notes on page 40 of the DER when describing "Key Model Choices and Assumptions" that "The patient population is assumed to exclude patients over 50 with increased cardiovascular risk, as JAK inhibitors will likely not be approved in that population." We disagree with including speculation such as this in ICER's evidence report and recommend its removal as this is a decision ultimately made by the FDA.

3. Inclusion of the cost-consequence analysis as a scenario analysis rather than as a base case analysis

As part of its base case analyses, ICER includes a cost-consequence model estimating the cost per patient-reported outcome (PRO). ICER includes one measure for itch (PP-NRS) and three measures for sleep (POEM, SCORAD, ADerm-IS), wherein the data are derived from a subset of manufacturer submissions. ICER also notes that the analysis was conducted for a specific PRO, only if the data were provided for each EASI responder category.

While we acknowledge the importance of measuring PROs in this specific patient population and have done so extensively in abrocitinib's JADE clinical program, we do not believe the cost-consequence analysis should be included as part of ICER's base case results for the following reasons:

- 1. In its description of the cost-consequence results, ICER notes that "the average incremental change in score over the five year time horizon is presented where data was available by health state, as no commonly meaningful threshold or translation for these measurements was identified." Without a common threshold for interpreting these results, it will be difficult for payers and policymakers to interpret the output and use it to make meaningful decisions when it comes to patient access, especially when reported in the same context as the cost-effectiveness (CE) results (i.e., cost per quality-adjusted life year [QALY] gained, health benefit price benchmarks [HBPB]).
- 2. Moreover, in a report by the National Institute for Health Research, the NHS notes that while cost-consequence analyses can present a broader range of health and non-health costs and benefits, there are a number of disadvantages; specifically, the NHS notes that cost-consequence analyses: (1) do not provide specific guidance on cost-effectiveness thresholds, (2) have limited generalizability given disaggregated outcomes and lack of common thresholds across outcomes, and (3) lack transparency for decision-making purposes.¹³

Given the above, we respectfully request that ICER move the cost-consequence analysis to the scenario analysis portion of the report and subsequently provide a meaningful interpretation of this analysis to aid patients, policymakers, and payers in understanding the outcomes and applicability to the AD treatment landscape.

4. Discontinuation probability of emollients

On page 41 of the DER, ICER notes that a per-cycle discontinuation probability of 25.40% was assumed for emollients/standard of care (SOC) in the CE model; this discontinuation probability is sourced from the ECZTRA 1 and ECZTRA 2 phase 3 clinical trials of tralokinumab.¹⁴

We have several criticisms of this input assumption in the CE model:

1. This discontinuation probability is only representative of the placebo arm from the trials of tralokinumab. Because there are other interventions compared to emollients/SOC in ICER's analysis, it is inappropriate to base the discontinuation probability off of one intervention's placebo arm. We respectfully request that ICER provide justification for why only the tralokinumab phase 3 clinical trials were considered to inform the emollients/SOC discontinuation rate.

2. The discontinuation probability from ECZTRA 1 & 2 (25.40%) is considerably lower than the SOC discontinuation rate assumed in ICER's 2017 evaluation of dupilumab (65.80%), wherein ICER assumed that discontinuation in the SOC arm was equivalent to the placebo arm of the dupilumab clinical trial. We recommend that ICER consider conducting a sensitivity analysis for the discontinuation probability assumed for the emollients/SOC arm of the CE model given the significant differential between these two rates.

5. Data inconsistencies

Pfizer has identified several inaccuracies and opportunities for clarification, listed in Appendix A with their exact location for ease of correction. We recommend these be addressed in the subsequent version of the Evidence Report.

6. Comments on Draft Voting Questions

As part of this review period, ICER also provided Draft Voting Questions in anticipation of the Policy Roundtable portion of the public meeting scheduled for July 23, 2021. After reviewing the questions, we have the following feedback:

- Question 9: States "Patients' ability to achieve major life goals related to education, work, or family life"; however, AD has a substantial impact on activities of daily living and other aspects of patients' and caregivers' lives beyond "major life goals". We recommend adding outcomes to the list to reflect "Patients' [caregivers'] ability to achieve day-to-day goals and activities."
- Question 11: We respectfully ask ICER to provide additional context and clarification around the intended interpretation of "health inequities." Participants in the Policy Roundtable have a wide variety of backgrounds and experiences and we are concerned the question may be too vague for interpretation.
- Question 12: We believe the question "What are the relative effects of the JAK inhibitors as a class versus dupilumab on patients' *ability to manage and sustain treatment given the complexities of the regimens*?", in particular the bolded language, is vague and leading in nature and therefore should be clarified and rephrased.
- Questions 15 & 16: We request that it be noted why only 2 of the 4 systemic therapies are included in this section of the Voting Questions (e.g., we assume it is because their prices are not publicly available at this time).

We respectfully ask that ICER acknowledge our feedback and make the necessary efforts to address these comments, so that patients, physicians, and other stakeholders can have an unbiased perspective from which to consider the value of newer treatments for AD. Pfizer welcomes the opportunity to discuss these recommendations further.

Sincerely,

Gergana Zlateva, PhD

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Appendix A

Original Wording	Section, Page Number, Line Numbers	Proposed Change
"JADE TEEN also enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 16 weeks ." "In the monotherapy trials, more patients experienced a ≥4-point improvement on the	3.1 Methods Overview Evidence Base - Moderate- to-Severe Population pg. 17, lines 16-18 3.2 Results for Moderate-to- Severe Population Clinical Benefits -	"JADE TEEN also enrolled patients 12-17 years and measured its co-primary endpoints of EASI 75 and IGA (IGA score of 0/1 and ≥2 points from baseline improvement) at 12 weeks. " Since the endpoint is ≥4-point improvement on the PP-NRS, we recommend clarifying the
patient reported Peak Pruritus Numerical Rating Scale (PP-NRS), a measure of itching, with abrocitinib 200 mg and 100 mg than with placebo (55%-64% and 38%-50% vs. 12%-26%, respectively."	Abrocitinib pg. 21, lines 34-35 and throughout where applicable	abbreviation as such (i.e., "PP-NRS4"), where applicable.
"One trial also measured Scoring Atopic Dermatitis (SCORAD), an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness."	3.2 Results for Moderate-to-Severe Population Clinical Benefits - Abrocitinib pg. 22, lines 12-14	"All abrocitinib trials included in ICER's assessment (JADE MONO-1, MONO-2, COMPARE, TEEN, Phase 2b) measured Scoring Atopic Dermatitis (SCORAD), an instrument combining objective measures of area and intensity with subjective symptoms including itch and sleeplessness. In the Phase 2b trial, there were greater reductions from baseline"
"In one trial, mean reductions on the Hospital Anxiety and Depression Scale (HADS) were statistically significantly greater with abrocitinib 200 mg and 100 mg doses than placebo for both depression and anxiety."	3.2 Results for Moderate-to-Severe Population Clinical Benefits - Abrocitinib pg. 22, lines 15-18	All abrocitinib trials included in ICER's assessment (JADE MONO-1, MONO-2, COMPARE, TEEN, Phase 2b) measured HADS. In addition to the results included from MONO-1, pooled results from the 3 monotherapy trials (MONO-1, MONO-2, Ph2b) have been reported in: Silverberg, J.I., Thyssen, J.P., Simpson, E.L. et al. Impact of Oral Abrocitinib Monotherapy

"Subgroup analyses based on disease severity at baseline mostly provided by manufacturers as academic-in-confidence suggest qualitatively better outcomes in patients with severe disease compared to those with moderate disease with abrocitinib, baricitinib, and tralokinumab (see Evidence Tables D3.29, D3.31, D3.33, D3.35-38, D3.40, D3.42, and D3.44-45). 39,45,67 No evidence stratified by disease severity was identified for upadacitinib."	3.2 Results for Moderate-to-Severe Population Subgroup Analyses and Heterogeneity Disease Severity pg. 28, lines 22-26	on Patient-Reported Symptoms and Quality of Life in Adolescents and Adults with Moderate-to-Severe Atopic Dermatitis: A Pooled Analysis of Patient-Reported Outcomes. Am J Clin Dermatol (2021). https://doi.org/10.1007/s40257-021-00604-9 Abrocitinib trials were not powered for stratification by baseline severity (we imagine this is the case for the other treatments as well). Therefore, that limitation should be explicitly stated here for proper context and interpretation.
	Results - Placebo-controlled Combination Trials in Children and Adolescents (Short- and Long-term) pg. 119	Recommend including JADE TEEN results in table D2.12., presented as oral presentations at the American Academy of Allergy Asthma & Immunology 2021 Annual Meeting, Feb 26 – Mar 1, 2021. Eichenfield LF, Flohr C, Sidbury R, et al. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): Results From the Phase 3 JADE TEEN Study. McMichael A, Cork M, Teng J, et al. Patient-Reported Outcomes (PROs) With Abrocitinib Treatment in

		Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): Results From the Phase 3 JADE TEEN Study.
JADE TEEN sample size by treatment arm	Table D3.3. Baseline Characteristics pg. 163	The sample sizes were reported in Eichenfield LF, Flohr C, Sidbury R, et al. Efficacy and Safety of Abrocitinib in Adolescent Patients With Moderate-to-Severe Atopic Dermatitis (AD): Results From the Phase 3 JADE TEEN Study. PBO = 96 ABRO 100 mg = 95
Row 1- Study of Abrocitinib Compared with Dupilumab in Adults with Moderate to Severe Atopic Dermatitis on Background Topical Therapy Pfizer NCT04345367 Estimated Completion Date - October 2, 2021	D4. Ongoing Studies pg. 296	ABRO 200 mg = 94 Last Update Posted: March 24, 2021 on ClinicalTrials.gov states "Estimated Study Completion Date: July 14, 2021"
Date – October 2, 2021	D5. Previous Systematic Reviews and Technology Assessments pg. 301	Recommend adding the recently published NMA due to its relevance and scope: Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, Cameron MC, Myers DE, Clibborn C, DiBonaventura M. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. J Eur Acad Dermatol Venereol. 2021 May 15. doi: 10.1111/jdv.17351. Epub ahead of print. PMID: 33991374.

June 11, 2021

Dr. Steven D. Pearson President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for atopic dermatitis (AD). AD is a lifelong, chronic condition with no current cure that impacts more than 9.6 million children and 16.5 million adults in the United States. It can have a huge impact on patients' quality of life causing severe itching and pain, which can lead to difficulty sleeping and lost productivity. It is imperative that the needs of these patients and the value treatments bring to them are being considered in any value assessment for AD. We encourage ICER to consider the following comments on its draft evidence report.

ICER's model is not sensitive to or reflective of the outcomes that matter most to patients.

In ICER's *Patient and Caregivers Perspective* section of the draft evidence report, it is clear that the primary symptom of concern for AD patients is itch. Patients express that itch can lead to a host of additional problems including skin pain and infections, as well as disrupting sleep and causing anxiety and depression. It is primarily through itch and pain, that AD can have a profound impact on life activities, interpersonal relationships, and the ability to be productive at work. Patients highlighted the need for therapies to address itch and pain that work quickly, provide sustained relief, and are safe for long-term use.

Other than discontinuation rate, none of these aspects of importance raised by patients was incorporated into the model. The cycle in the model was 16-weeks, so any benefit from a therapy that resulted from a quick response as compared to a slower or delayed response would be missed in the ICER model. Similarly, long-term data was not used in the construction or execution of the ICER model. We would encourage ICER to rework the model to ensure the benefit of expedient relief is captured.

¹ https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/

Despite the emphasis patients put on the importance of itching on their quality of life, the ICER model is structured solely around Eczema Area and Severity Index (EASI) score, which combines coverage, location and severity weighted equally by clinicians – not patients. Recent studies have suggested that itch-specific measures have weak-to-moderate correlations with EASI.² There are more sensitive resources available that do capture a more accurate picture of the patient's experience with itch and pain, and we would encourage ICER to look to these for its model. For example, the model could be built on a combination of EASI and PP-NRS or used patient itch questionnaire - numerical rating scale and verbal rating scale (PIQ NRS, VRS)³ or frequency of itch.⁴

For example, ICER states that more patients achieved a ≥4-point improvement in PP-NRS with upadacitinib 30 mg than dupilimumab (55% vs. 36%). But since the ICER model is based solely on response as defined by change in EASI score, upadacitinib is considered to be 'less effective' than dupilimumab. Subsequently upadacitinib has almost twice the efficacy of the comparator in terms of the one outcome that matters most to patients but still the model shows these two treatments to at best be equal in efficacy, and at worse, less effective than the comparator. We would highly encourage ICER to rework its modeling to ensure it is capturing the outcomes that matter most to patients.

ICER's model continues to use the discriminatory Quality-Adjusted Life Year (QALY) and relies on population averages and does not take into account patient heterogeneity.

We would like to reiterate that the QALY innately discriminates against people with disabilities and chronic illnesses and is an inappropriate tool for assessing value. We would encourage ICER to look to more sensitive mechanisms that do not rely on population level averages and do a better job incorporating the outcomes that matter to the specific patient population in question.

In addition to its reliance on the QALY, ICER compares all treatments it is assessing to placebo or dupilimumab, under the assumption that both the index and comparator drugs are similarly effective for each patient. This is an example of when the value assessments only looking at the "average" patient will not reveal accurate or useful information on actual efficacy of treatments. For many patients dupilimumab will not

² Silverberg JI, Lai JS, Patel KR, Singam V, Vakharia PP, Chopra R, Sacotte R, Kantor R, Hsu DY, Cella D. Measurement properties of the Patient-Reported Outcomes Information System (PROMIS®) Itch Questionnaire: itch severity assessments in adults with atopic dermatitis. British Journal of Dermatology. 2020 Nov;183(5):891-8.

³ Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, Augustin M, Szepietowski JC, Ständer S. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta dermato-venereologica. 2012 Sep 1;92(5):502-7.

⁴ Oosterhaven JA. How to measure itch in atopic dermatitis?. The British Journal of Dermatology. 2020 Nov 1:183(5):802-3.

⁵ RINVOQ™ (upadacitinib) Achieved SuperiorityVersus DUPIXENT® (dupilumab) For Primaryand All Ranked Secondary Endpoints in Phase3b Head-to-Head Study in Adults with AtopicDermatitis [press release]. 2020
⁶ NCD Report



work, will stop working after treatment initiation, or will be discontinued due to side effects. For all three of these groups, the comparison to dupilimumab is irrelevant. We would encourage ICER to abandon its reliance on population level averages and address the question of value from the perspective of patients who have very particular needs from their treatments.⁷

ICER's inputs are opaque, and we would encourage more transparency.

The cost-effectiveness calculations in ICER's model are largely driven by the choice and application of the health utility weights within the QALY. In the past ICER has been urged by various stakeholders to be more transparent. Unfortunately, this specific report seems to take a step backwards and is less transparent than many previous reports, as many of its inputs are blacked out. It is very difficult for stakeholders to make comments on data choices we cannot clearly see. We would encourage ICER to be transparent about its choice of utilities and make a concerted effort to share more, not less, data with stakeholders as it continues performing assessments.

ICER uses randomized clinical trial data when real world estimates of utilities for health states, particularly for active disease, are likely to be more representative of the population of need.

As a general rule, real-world cohort-based estimates of utilities, especially for active disease states (non-response) will provide more accurate data than relying on randomized clinical trial data. Clinical trials are known to recruit healthier patients than those people who make up the real-world population of need. There is also the problem of the placebo effect in randomized clinical trials on patients in the comparator arm. Finally, patients in RCTs tend to receive far more non-treatment specific care and attention; symptom management, and interaction with clinicians than the average patient in a real-world setting. As such, quality of life measures in patients non-

⁷ Basu A, Grieve R, Pritchard D, Stevens W. One size does not always fit all in value assessment. Am J Manag Care. 2019 Nov 1;25(11):540-2.

⁸ Hay JW. Now is the time for transparency in value-based healthcare decision modeling. Value in Health. 2019 May 1;22(5):564-9.

⁹ Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, Dieppe P. The causes and effects of sociodemographic exclusions from clinical trials. Health Technology Assessment (Winchester, England). 2005;9(38):iii-152.

¹⁰ Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, Brophy J, Rossignol M. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. American journal of epidemiology. 2007 Nov 15;166(10):1203-9.

¹¹ Hussain-Gambles M, Atkin K, Leese B. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. Health & social care in the community. 2004 Sep;12(5):382-8.

¹² Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Statistics in medicine. 1990 Nov:9(11):1259-76.

¹³ West J, Wright J, Tuffnell D, Jankowicz D, West R. Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol. BMJ Quality & Safety. 2005 Jun 1;14(3):175-8.

response states are often higher for patient in randomized clinical trials than in real world cohort studies.

Given the availability of real-world estimates of utilities, we would encourage ICER to use this available data instead of relying on utilities from randomized clinical trials. Literature based values for utilities have been preferred in the vast majority of AD models produced in the last decade. A recent review of studies measuring health utility weights in AD patients showed a fairly consistent conclusion that untreated moderate to severe AD had a fairly consistent estimate of 0.61.

Conclusion

PIPC echoes some of our consistent feedback in this comment letter urging ICER to be more transparent, incorporate outcomes that truly matter to patients, and account for patient heterogeneity.

Sincerely,

Tony Coelho Chairman

Partnership to Improve Patient Care

Ty Coelho

¹⁴ Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Fuxench ZC, Simpson EL. Health utility scores of atopic dermatitis in US adults. The Journal of Allergy and Clinical Immunology: In Practice. 2019 Apr 1;7(4):1246-52.

¹⁵ Lundberg L, Johannesson M, Silverdahl M, Hermansson C, Lindberg M. Quality of life, health-state utilities and willingness to pay in patients with psoriasis and atopic eczema. British Journal of Dermatology. 1999 Dec;141(6):1067-75.

Schmitt J, Meurer M, Klon M, Frick KD. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. British Journal of Dermatology. 2008 Feb;158(2):351-9..
 Capucci S, Hahn-Pedersen J, Vilsbøll A, Kragh N. Impact of Atopic Dermatitis and Chronic Hand Eczema on Quality of Life Compared With Other Chronic Diseases. Dermatitis. 2020 May 1;31(3):178-84.

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Submitted via email: publiccomments@icer.org

RE: Draft Evidence Report for the Assessment of "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis"

Dear ICER Review Team:

Sanofi/Regeneron Pharmaceuticals alliance appreciates the opportunity to provide comments on ICER's draft evidence report titled "JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis" in which dupilumab (DUPIXENT®) is included as a comparator.

As previously communicated, since dupilumab's initial approval in 2017 for the treatment of adults with moderate-to-severe atopic dermatitis (AD), real-world studies have consistently demonstrated its long-term efficacy, safety and treatment persistence in adults, children (aged \geq 6 to <12 years) and adolescents (aged \geq 12 to <18 years). ^{12,3} This body of evidence provides clinicians with the confidence and ability to use dupilumab as indicated in the treatment of patients with AD.

We recently became aware that ICER updated the network meta-analysis (NMA) presented in the draft evidence report to use a multinomial methodology. Please see our suggested recommendations on the methodological appropriateness of the new analysis and a summary of key observations on the current draft evidence report (table below).

¹ Beck LA, Thaci D, Deleuran M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 Years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2020;21(4):567 –577.

² Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol*. 2020;182(1):85 –96.

 $^{^{3}}$ Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *Br J Dermatol*. 2021;184(5):857 –870.

KEY OBSERVATIONS

- As it remains unknown which doses of the JAK inhibitors will be approved by the FDA, Sanofi/Regeneron recommend that ICER acknowledge this uncertainty and include a caveat when presenting the results of the updated NMA. For instance, a draft report of the upadacitinib HEADS-UP study, in which 30 mg was the only dose evaluated, was added to the report's NMA. It is currently unknown if this dose will be approved by the FDA. Should the final approved dose not be 30 mg, this could impact the NMA findings. We recommend that ICER acknowledge the possibility that the NMA results will not be valid if a dose is not approved by the FDA.
- Sanofi/Regeneron believe that the multinomial model is not appropriate for the NMA. A multinomial model may be used to address possible abnormal estimates across Eczema Area and Severity Index (EASI) response thresholds. Abnormal estimates may be due to the independent modelling of the categories and/or due to high missing data on any given EASI responses. In this particular NMA, there are no such issues, therefore we do not see the justification for the multinomial model. Further, the disadvantage of the multinomial model is the strong assumption that the treatment effect of achieving each EASI response threshold is the same across all EASI cut-offs, that is, the model assumes that the relative increase in an EASI-75 response would be exactly the same for an EASI-50 or EASI-90 responses. This is an influential assumption that is not supported by the evidence from the individual studies. The attempt to increase precision using a multinomial model in this case is inappropriate and the point estimates could be biased. Sanofi /Regeneron recommend that ICER models the EASI responses separately, as was done in the first ICER NMA draft report.
- Sanofi/Regeneron agree with ICER that safety is of utmost importance when assessing the
 value of treatments for AD. Dupilumab's long-term safety has been well established, in
 both children as young as six years of age and adults. This is supported by a robust and
 ever-growing body of real-world evidence, as well as widespread use in clinical practice.^{4,5,6}
- Sanofi/Regeneron agree that long-term safety is critical and needs be supported by long-term evidence. Therefore, we do not agree with speculative statements included in the report referring to the safety of treatments evaluated. For example, on page 29, ICER states "though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data may also apply to tralokinumab". This statement is not supported by evidence. We recommend deleting this sentence from the report.

⁴ Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol*. 2020;182(1):85–96.

⁵ Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged \geq 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *Br J Dermatol*. 2021;184(5):857–870.

⁶ Beck LA, Thaci D, Deleuran M, et al. Dupilumab provides favorable safety and sustained efficacy for up to 3 years in an open-label study of adults with moderate-to-severe atopic dermatitis. *Am J Clin Dermatol*. 2020;21(4):567–577.

- Given ICER's recognition of the importance of long-term safety, Sanofi/Regeneron disagree with the exclusion of adverse events in the cost-effectiveness evaluation. Ignoring adverse events as a factor in the cost-effectiveness analyses may underestimate the cost and overestimate the benefit of treatments associated with important safety concerns.
 Sanofi/Regeneron recommend that ICER takes into account important adverse events observed with JAK inhibitors as described in the boxed warnings of their US prescribing information⁷⁸: serious infections, malignancy and thrombosis.
- Sanofi/Regeneron believe that, in addition to long-term safety, the long-term efficacy and durability of effect of treatments for AD should be demonstrated in clinical practice. As the standard of care in AD, dupilumab's long-term efficacy is well established and further supported by real-world evidence.⁹
- Sanofi/Regeneron agree with ICER's acknowledgement of the importance of type 2 coexisting diseases in AD and the recognition that dupilumab "has proven efficacy in treating certain patients with asthma or chronic rhinosinusitis". 10,11
- Sanofi/Regeneron are **committed to ensuring patient access and to responsible pricing** practices that reflect the value of dupilumab as recognized by the ICER 2017 report.

⁷ RINVOQ™ (upadacitinib) prescribing information. Sligo, Ireland: AbbVie Ireland NL B.V.; August 2019.

⁸ OLUMIANT (baricitinib) prescribing information. Lilly USA, LLC: Indianapolis, IN, USA; May 2018.
⁹ Ariëns LFM, van der Schaft J, Spekhorst LS, Bakker DS, et al. Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-week results from the Dutch BioDay registry. *J Am Acad Dermatol*. 2021;84(4):1000-1009
¹⁰ Hamilton JD, Harel S, Swanson BN, Brian W, Chen Z, Rice MS, Amin N, Ardeleanu M, Radin A, Shumel B, Ruddy M, Patel N, Pirozzi G, Mannent L, Graham NMH. Dupilumab suppresses type 2 inflammatory biomarkers across multiple atopic, allergic diseases. *Clin Exp Allergy*. https://doi.org/10.1111/cea.13954

¹¹ Boguniewicz M, Beck LA, Sher L, et al. Dupilumab improves asthma and sinonasal outcomes in adults with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol Pract*. 2021;9(3):1212–1223.

DETAILED COMMENTS AND RECOMMENDATIONS

Suggestions for change are highlighted in red.

Page	Original text	Suggestions for Text Changes or Comments
8	A number of new biologic therapies are available	Comment:
	or being evaluated in patients with atopic	This statement erroneously implies that JAK
	dermatitis.	inhibitors are considered biologics.
		In contrast with JAK inhibitors, which are generally
		considered to be broad immunosuppressants,
		dupilumab is a targeted immunomodulator.
		Recommendation:
		Reword statement to reflect the fact that JAK
		inhibitors are not biologic therapies: "A number of
		new therapies are being evaluated in patients with
		atopic dermatitis."
9	A topical JAK inhibitor, ruxolitinib cream, is being	Comment:
	evaluated for patients with mild-to-moderate	The statement does not include the caveat that
	atopic dermatitis.	ruxolitinib, as well as the rest of the interventions
		included in the report, are yet to be approved by the FDA at the time of this evaluation.
		the FDA at the time of this evaluation.
		Recommendation:
		Please include the following caveat: "As of the
		writing of this report, other than dupilumab
		(which was approved in 2017 for atopic
		dermatitis), none of the other drugs at any dose
		(abrocitinib, baricitinib, tralokinumab,
		upadacitinib, ruxolitinib) have been approved by
		the FDA for this indication."
9	Quantitative indirect comparisons across the new	Comment:
	agents and dupilumab, as well as head-to-head	Neither upadacitinib and abrocitinib are approved
	comparisons between two of the agents (upadacitinib and abrocitinib) and dupilumab	by the FDA, and it remains unknown which doses will ultimately be approved.
	suggest that higher doses of upadacitinib and	will ditilifiately be approved.
	abrocitinib (at the doses likely to be approved)	Recommendation:
	may be somewhat more effective than dupilumab,	Suggest ICER acknowledge that it remains
	while baricitinib (at the doses likely to be	unknown which doses will be approved by the
	approved) and tralokinumab are likely somewhat	FDA. The text noting "at doses that are likely to be
	less effective than dupilumab;	approved" and the statement should be amended
		as follows:
		"Quantitative indirect comparisons across the new
		agents and dupilumab, as well as head-to-head
		comparisons between two of the agents
		(upadacitinib and abrocitinib) and dupilumab
		suggest that higher doses of upadacitinib 30 mg
		and abrocitinib 200 mg (final dosing yet to be
		approved by the FDA) may be somewhat more
		effective than dupilumab, while baricitinib (final

dosing yet to be approved by the FDA) and tralokinumab are likely somewhat less effective than dupilumab;" Further, the specific doses upon which these conclusions are drawn should be inserted into the text throughout the report, given that no doses are currently approved by the FDA. It is important that this information is contained within the Executive Summary, as not all key stakeholders will read the report in its entirety. Please also note the typo in upadacitinib. Comment: This statement erroneously implies that JAK inhibitors are considered biologics. In contrast with JAK inhibitors, which are generally considered to be broad immunosuppressants, dupilumab is a targeted immunomodulator. Recommendation: Please revise statement to: "Safety is an important consideration with new therapies and" Recommendation: Please correct the typo in the last row of Table ES3 to read that upadacitinib (versus dupilumab) is Dominated (More Costly and Less Effective). We also suggest adding this terminology to Table 4.10. Comment: This sentence seems incomplete. The mechanism of action for dupilumab and tralokinumab are different. Therefore, the long-term safety data collected for dupilumab through its extensive research program cannot be assumed to be relevant to tralokinumab. Recommendation: We suggest that this sentence be removed from the report. We suggest that this sentence be removed from the report. Base-case costs included direct medical costs by health state, drug costs and any costs associated with administration or monitoring.			
## Though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data for dupilumab may also apply to tralokinumab. ### Though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data for dupilumab may also apply to tralokinumab. #### Though dupilumab is an IL-4 receptor alpha antagonist, it inhibits IL-4 and IL-13 signaling and suggests that long-term safety data for dupilumab may also apply to tralokinumab. ###################################			
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44 Table 4.7 Direct Medical Health State Costs			

 $^{^{12}}$ DUPIXENT $^{\$}$ (dupilumab) prescribing information. Tarrytown, NY, USA: Regeneron Pharmaceuticals, Inc.; January 2021.

		In addition, the monitoring costs included in the current model are inconsistent with ICER's previous approach when evaluating the same class of products in rheumatoid arthritis. Specifically, the 2019 ICER review of Janus Kinase Inhibitors forRheumatoid Arthritis ¹³ included quarterly drug monitoring costs for tuberculosis tests, comprehensive metabolic test panels, lipid panels and acute hepatitis panels (Table 4.11).
		Recommendation: Given that dupilumab does not require on-going monitoring, those costs should be removed from the cost-effectiveness model.
		In order to be consistent with previous reviews of JAK inhibitors, we also suggest that quarterly drugmonitoring costs, as described above, be included for JAK inhibitors in the cost-effectiveness model of AD.
41	Table 4.3 Discontinuation Rates	Comment: To inform the drug specific discontinuation rates in the economic model, ICER currently uses a combination of data sources, using discontinuation rates from randomized controlled trials (JAK inhibitors) to inform discontinuation rates in the first year of the model, as well as open label extension studies (dupilumab) as an input for the second and subsequent years. This may be due to the lack of long-term published data for some of the newer interventions.
		Recommendation: We would like to caution ICER that the current stratification of drug-specific discontinuation rates between year 1 and years 2+ has the potential to bias the findings against the drug with the longer duration of follow-up (in this case dupilumab), if the discontinuation rate is assumed to increase with time. The simplest solution to this problem would be to use one annual rate of discontinuation, instead of two, that is derived from clinical trials with a similar duration of follow-up
		clinical trials with a similar duration of follow-up for each drug, e.g., 52 weeks. Specifically, for dupilumab, we suggest using the same approach as in the 2017 review of atopic dermatitis, where

¹³ Tice J, Kumar V, Chapman R, Walsh J, Herron-Smith S, Cianciolo L, Bradt P, Pearson S. Janus kinase inhibitors for rheumatoid arthritis: effectiveness and value. Institute for Clinical and Economic Review. Last Updated November 26, 2019. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_RA_Evidence_Report_112619-2.pdf

the annualized discontinuation rate (2.15% per 16-week-cycle) was take and SOLO-2.14 52 Specifically, tralokinumab dosing may include an option for every four weeks instead of every two-week dosing, which would lower treatment costs. It remains unknown whether a differ interval will be approved by the FDA Recommendation: We suggest to change wording to "Sometime treatment costs. Accurate assessment efficacy would also need to be adjusted accordingly in the model." This will list with ICER's acknowledgment that "complexity with ICER's acknowledgment that "complexity of care". Table 6.2 Potential Other Benefits or Disadvantages Row 3: Patients' ability to manage and sustain treatment given the complexity of regimen the annualized discontinuation rate (2.15% per 16-week-cycle) was take and SOLO-2.14 Comment: It remains unknown whether a differ interval will be approved by the FDA Recommendation: We suggest to change wording to "Sometime very two-weeks, which would pote treatment costs. Accurate assessment efficacy would also need to be adjusted accordingly in the model." This will list with ICER's acknowledgment that "similar but slightly worse than for the on the higher dose". Comment: The report states that "the potentiant the rapies such as abrocitinib, baricity upadacitinib to improve outcomes for with atopic dermatitis may decrease complexity of care".	n from SOLO-1
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The complexity of a treatment regin	
	nen, and any
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There is an additional complexity fo	providers
when choosing a treatment regimer	for atopic
dermatitis. As stated in the report o	n page 41, JAK
inhibitors could affect mortality in p	atients over
the age of 50 years with a cardiovas	cular risk
factor, and therefore would not be o	considered
candidates. The boxed warnings of J	AK inhibitors
require clinicians to carefully consid	er the
contraindications when prescribing.	
Finally, in the context of treatment of	omnlovity we
also recommend that ICER consider	
initial and continued lab monitoring	any necessary
needed with JAK inhibitors, as in pre	any necessary that may be
reports. ¹⁵	any necessary that may be

 $^{^{14}}$ Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–2348.

¹⁵ Tice J, Kumar V, Chapman R, Walsh J, Herron-Smith S, Cianciolo L, Bradt P, Pearson S. Janus kinase inhibitors for rheumatoid arthritis: effectiveness and value. Institute for Clinical and Economic Review. Last Updated November 26, 2019. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_RA_Evidence_Report_112619-2.pdf.

		Recommendation: This statement should be amended to also include dupilumab, as dupilumab may reduce the complexity of care versus topical therapies as demonstrated by high persistency in real word studies. ¹⁶ ¹⁷
314	We extended the model time horizon from 5 years to lifetime in this scenario to capture longer term value, though we note that only one line of treatment was modeled in order to focus on the comparisons of interest	Comment: As noted by the FDA in the boxed warning for the class, there are rare but serious adverse events of interest that occur with JAK inhibitor use. 18,19 While ICER "did not find evidence of serious adverse events occurring in >5% of subjects among any of the clinical trials" (page 45), the clinical trials informing the efficacy in this model were of short duration and may not capture the less frequent but more significant adverse events such as serious infections, malignancies and thromboses included in the label of some of the agents of interest. 14,15
		Recommendation: While adverse events should ideally be included in all cost-effectiveness analyses, we suggest that ICER include a limitation to the base case analysis acknowledging that the exclusion of adverse events may introduce bias against products with favorable safety and tolerability profiles.
		Additionally, in the scenario analysis of the lifetime time horizon, the longer-term serious adverse events, regardless of incidence, should be considered given their significance and impact. If data in atopic dermatitis is not available to inform the long-term safety, we suggest that ICER may consider information from other conditions where they are better characterized.

We appreciate the opportunity to be involved in this review and look forward to a continued dialogue with ICER.

¹⁶ Silverberg JI, Guttman-Yassky E, Gadkari A, et al. Real-world persistence with dupilumab among adults with atopic dermatitis. Ann Allergy Asthma Immunol. 2021 Jan;126(1):40-45.

¹⁷ Eichenfield LF, DiBonaventura M, Xenakis J,et al. Costs and Treatment Patterns Among Patients with Atopic Dermatitis Using Advanced Therapies in the United States: Analysis of a Retrospective Claims Database. Dermatol Ther (Heidelb). 2020 Aug; 10(4): 791–806.

¹⁸ RINVOQ[™] (upadacitinib) prescribing information. Sligo, Ireland: AbbVie Ireland NL B.V.; August 2019.

¹⁹ OLUMIANT (baricitinib) prescribing information. Lilly USA, LLC: Indianapolis, IN, USA; May 2018.

Mahf.

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Regeneron

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