Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value

Public Meeting – May 25, 2017

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

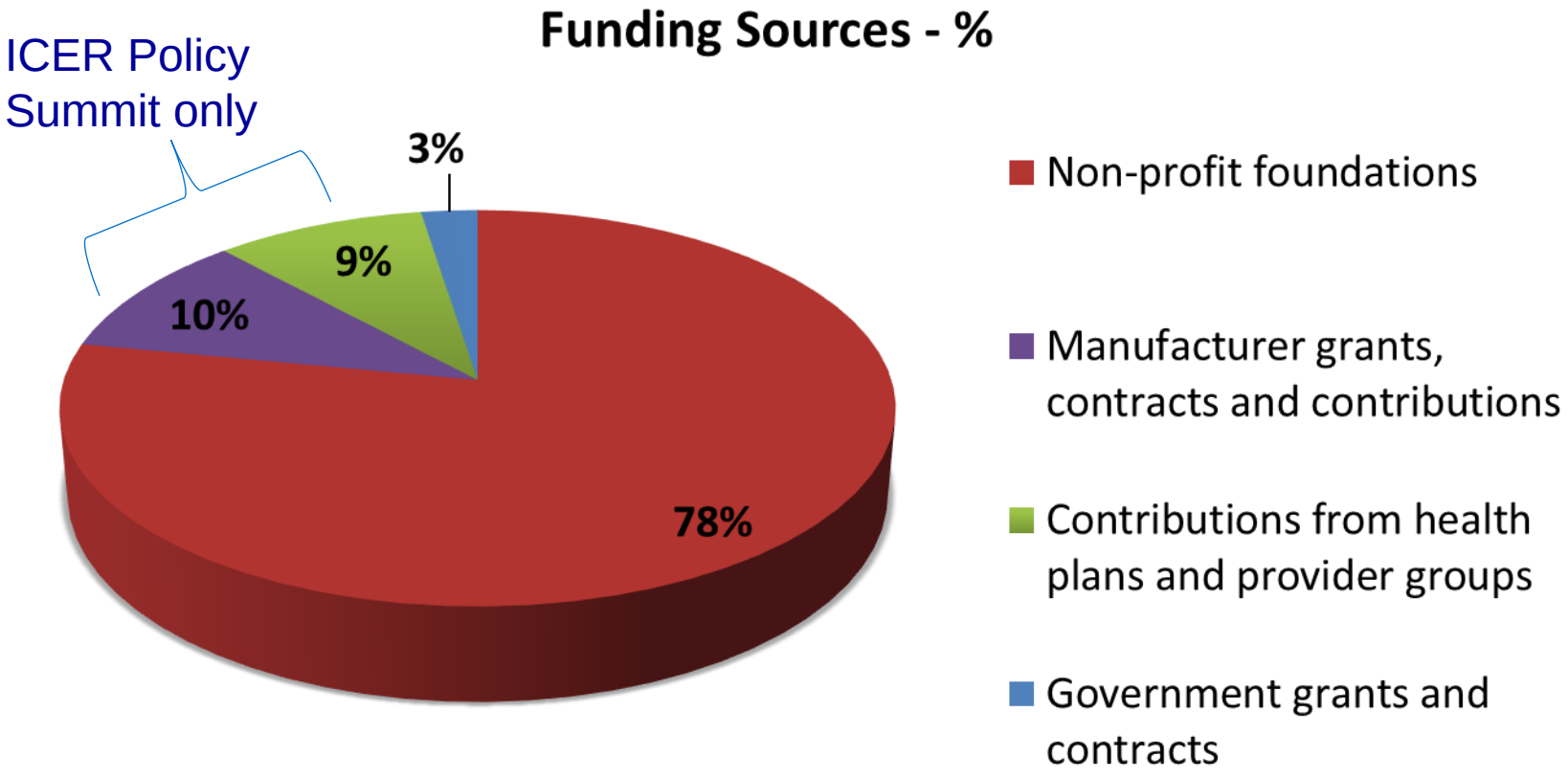
Welcome and Introduction

- Midwest Comparative Effectiveness Public Advisory Council (CEPAC)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2017

ICER Policy Summit only



Welcome and Introduction

- **Why are we here today?**
  - Innovation promising substantial benefits to patients and their families

    - "Its symptoms and extensive comorbidities result in a tremendous burden on patients and society in terms quality of life, social, academic, and many other consequences. The physical aspects of the disease include not only itching and scratching, but also sleep, pain, bleeding and dietary limitations. Patients with AD suffer from tremendous emotional consequences such as behavioral problems, irritability, crying, and social isolation. "

      -- International Eczema Council

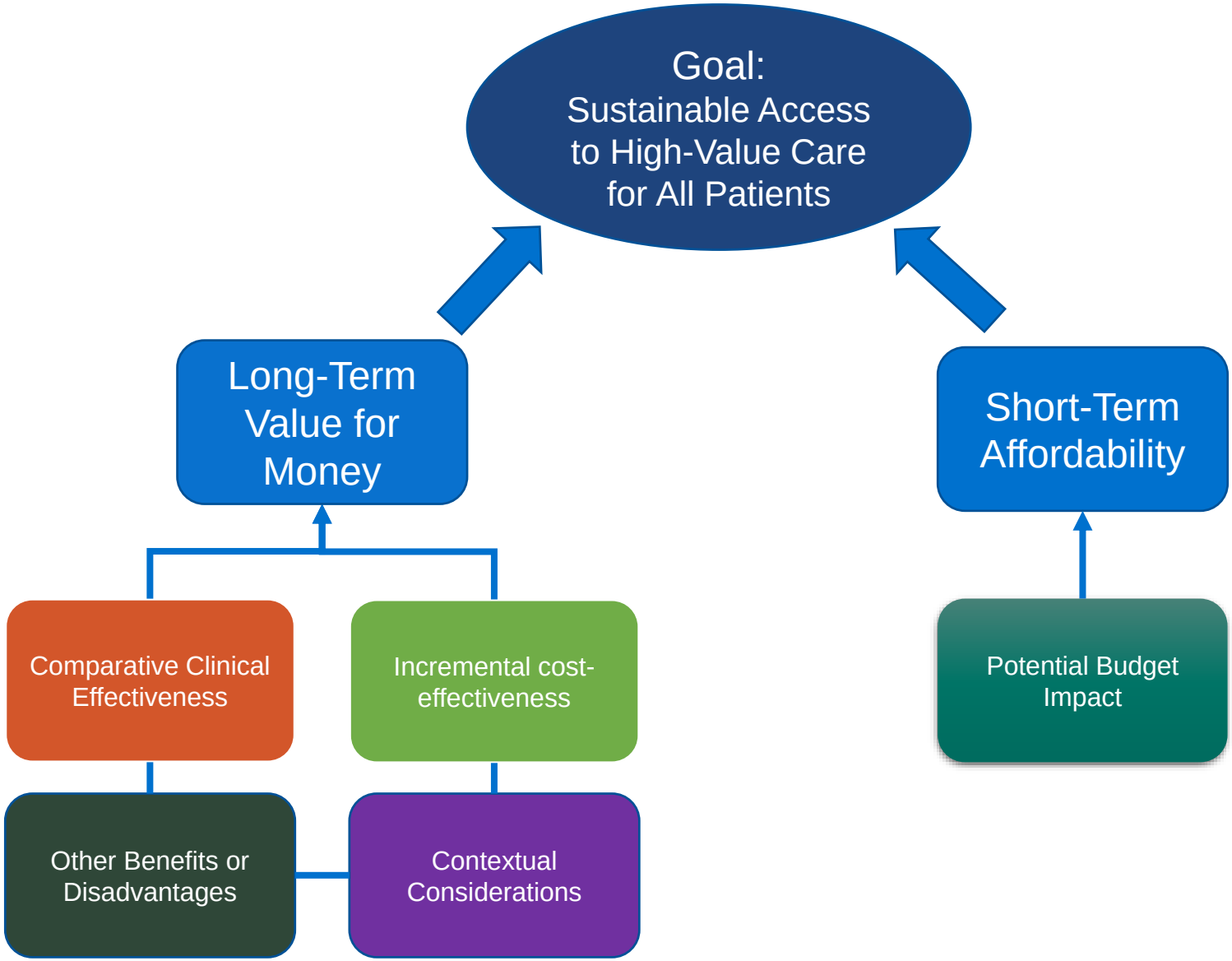
Welcome and Introduction

- **Why are we here today?**
  - Increasing health care costs affecting individuals, state and federal budgets
  - Atopic dermatitis a common condition with varying levels of severity
  - New mechanisms of action often raise questions about appropriate use, cost
  - Patients can have difficulty accessing drugs
    - Step therapy protocols
    - Requirements to switch drugs with new insurance
    - High out-of-pocket costs
  - Need for objective evaluation and public discussion of the evidence on effectiveness and value

Welcome and Introduction

How was the ICER report on treatments for atopic dermatitis developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Clinical expert report reviewers
  - Jonathan Silverberg, MD, PhD, MPH
  - Elaine Siegfried, MD
- How is the evidence report structured to support CEPAC voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

10:00am: Welcome and Opening Remarks

10:15 am: Presentation of the Evidence

Evidence Review: David Rind, MD, MSc, ICER

Comparative Value: Marita Zimmerman, MPH, PhD, University of Washington

11:30 am: Manufacturer Public Comment and Discussion

12:00 pm: Public Comments and Discussion

12:30 pm: Lunch

1:00 pm: Midwest CEPAC Deliberation and Votes

2:15 pm: Policy Roundtable

3:45 pm: Reflections and Wrap Up

4:00 pm: Meeting Adjourned

Evidence Review

David Rind, MD, MSc

Chief Medical Officer

Institute for Clinical and Economic Review

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Disclosures:

I have no conflicts of interest relevant to this report.

Key review team members:

Margaret Webb

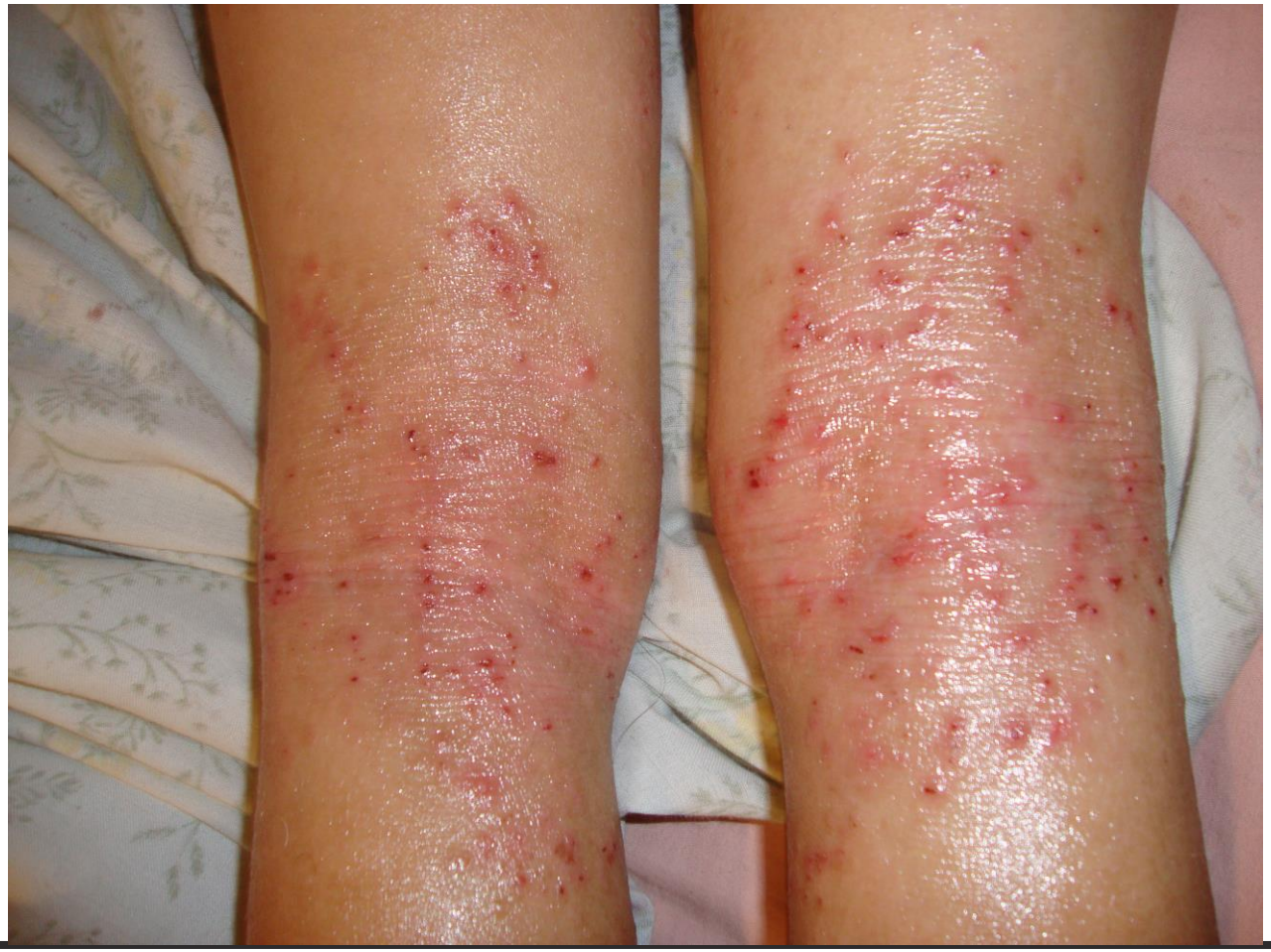
Shanshan Liu, MS, MPH

Noah Mwandha

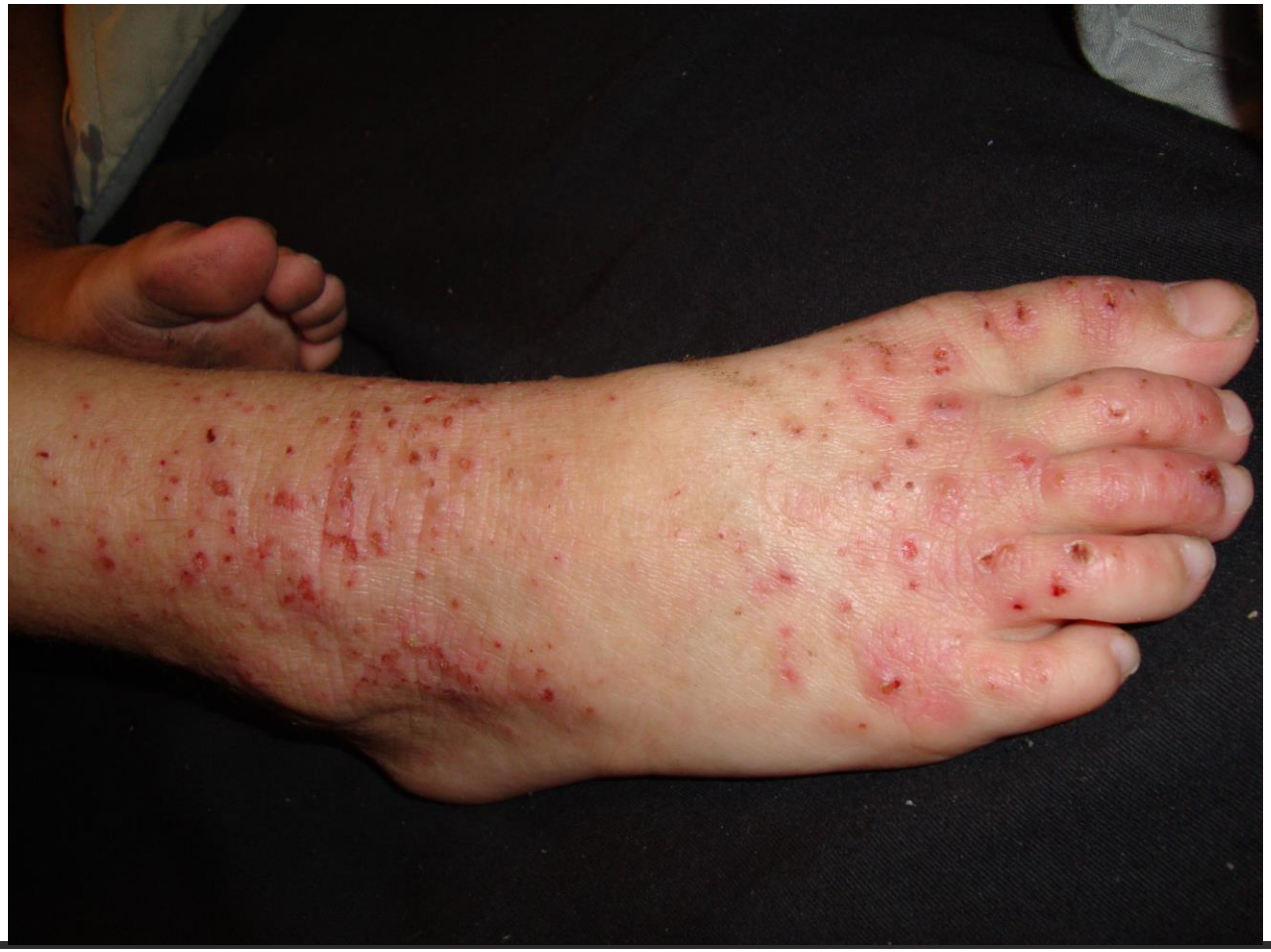
Topic in Context

- Chronic/chronically-relapsing skin condition characterized by itching and dry skin
- Affects approximately 11% of children and 3-7% of adults in the US
- Broad spectrum of disease; majority of patients managed adequately with topical therapies
- No agreed on definitions of “mild-to-moderate” or “moderate-to-severe”

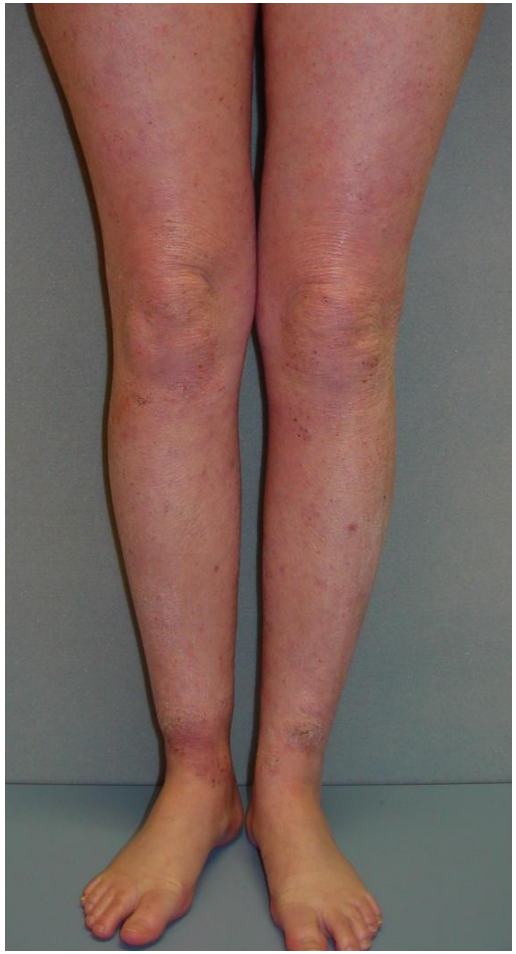
Moderate-to-Severe Disease



Moderate-to-Severe Disease



Moderate-to-Severe Disease



Effect on lives can be profound

- Itch, pain, sleep disruption
- Depression, anxiety, suicidal ideation
- Intimacy, family dynamics, bullying of children
- School and work attendance, presenteeism, disability for certain professions
- Diet, exercise, recreation
- Burdens of treatment
- Burdens for families/caregivers including lost sleep and missed work

Management

- Meticulous skin care, bland moisturizers
- Topical corticosteroids or calcineurin inhibitors if needed
- Not responding adequately to topical treatment:
  - Phototherapy
  - Systemic immunomodulators (none previously with FDA approval for this indication)
  - Prednisone

Harms of therapies

- Topical corticosteroids
  - Skin changes
  - Adrenal suppression
  - Steroid phobia
- Topical calcineurin inhibitors
  - Stinging
  - Black box warning for skin cancers and lymphoma
- Systemic immunotherapies
  - Infections, malignancies, blood dyscrasias, liver and kidney damage
- Phototherapy
  - Time
  - Risk of skin cancer
- Prednisone

Scope of the Review

- Crisaborole
  - Population: Adults and children with mild-to-moderate atopic dermatitis
  - Comparators: Topical therapies
- Dupilumab
  - Population: Adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies are medically inadvisable
  - Comparators: Topical therapies, phototherapy, or cyclosporine; primary comparison is to continuing failed topical therapies alone

Investigator's Global Assessment

- Various flavors and abbreviations
  - ISGA in the crisaborole trials
  - IGA in the dupilumab trials
  - Static assessment despite this in both
- Five point scale (0 to 4):
  - Clear; Almost Clear; Mild; Moderate; Severe
- Six point scale (0 to 5):
  - Clear; Almost Clear; Mild; Moderate; Severe; Very Severe
- Likelihood of achieving IGA of clear or almost clear (with or without ≥2 point improvement)

Issues of Focus for Crisaborole

Evidence for Crisaborole

- Two publications relating to 3 RCTs of crisaborole
- Two key trials AD301 and AD302
  - Identically designed 4-week phase III RCTs
  - 1522 patients analyzed
- Murrell 2015
  - 6 week trial in 25 patients (all patients received active and control treatment on different lesions)

Key Trial Results

- AD-301 and AD-302 randomized 2:1 (crisaborole n=1016; placebo n=506)
- Proportion of patients with ISGA of 0 or 1 and an improvement of 2 or more grades from baseline
  - 32.1% vs. 21.7%; $p<0.0001$
- Proportion of patients with pruritus score of 0 or 1 and an improvement of 1 or more grades
  - Day 8: 58% vs. 42%; $p<0.001$
  - Day 15: 60% vs. 44%; $p<0.001$
  - Day 22: 61% vs. 48%; $p<0.001$
  - Day 29: 63% vs. 53%; $p=0.002$

Comparing Crisaborole to Other Topicals

- No head-to-head data
- Two older RCTs of pimecrolimus used static IGA (with a 6-point scale) as an endpoint

	Clear	Almost clear	Mild	Moderate	Severe	Very severe
Crisaborole						
Pimecrolimus						

- Trials were published in 2002 and 2003
- Pimecrolimus is less effective than topical tacrolimums 0.1% or higher potency topical corticosteroids

Baseline Severity Across Trials

Trial	IGA score (%)		Mean body surface area involved (%)
	Mild	Moderate	
AD-301			
Crisaborole	39.0	61.0	18.8
Vehicle	36.3	63.7	18.6
AD-302			
Crisaborole	38.4	61.6	17.9
Vehicle	40.0	60.0	17.7
Ho 2003			
Pimecrolimus	32.5	67.5	NR
Vehicle	33.3	66.7	NR
Eichenfield 2002			
Pimecrolimus	30.0	60.3	26.1
Vehicle	31.6	57.4	25.5

Network Meta-analysis

Treatment	IGA 0/1
Crisaborole vs. placebo	1.57 (0.27-3.98)
Pimecrolimus vs. placebo	2.59 (0.98-4.44)
Crisaborole vs. pimecrolimus	0.61 (0.10-2.28)

Caveats

- Very wide credible intervals
- Slightly different outcome measures
- Performed many years apart
- Vehicle “placebo” may have been much better in crisaborole trials than in pimecrolimus trials

Harms

- Crisaborole was generally well tolerated
- Application site pain occurred in 4.6% of patients compared with 1.7% treated with vehicle

Controversies and Uncertainties

- No trials of crisaborole against an active comparator
- Safety is a major purported benefit of crisaborole, however the main evidence comes from two trials with 1016 patients receiving crisaborole for 28 days

Crisaborole Summary

- Inadequate evidence relative to topical corticosteroids and calcineurin inhibitors
- Probably less burning/pain than with topical calcineurin inhibitors
- Long-term safety uncertain
- Given uncertainties about benefits and safety, rated I (“Insufficient”) versus other topical therapies

Issues of Focus for Dupilumab

Evidence for Dupilumab

- Five randomized trials with 16-week outcomes
  - Three key trials: Thaci, SOLO 1&2 comparing dupilumab with placebo
  - Two trials with only limited reporting, including LIBERTY AD CHRONOS performed in patients receiving background topical corticosteroids (full results from LIBERTY AD CHRONOS were published in May 2017)
- Three additional trials (in asthma and nasal polyposis) to examine harms

Overall effect compared with placebo

- IGA (Investigator's Global Assessment)
  - Clear; Almost Clear; Mild; Moderate; Severe
  - Likelihood of achieving IGA of clear or almost clear (with or without ≥2 point improvement)

IGA Response Rates at 16 Weeks

Trial	IGA 0 or 1 and ≥ 2 reduction from baseline (%)			IGA 0 or 1 (%)		
	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo	Dupilumab 300 mg QW	Dupilumab 300 mg Q2W	Placebo
SOLO 1	**37**	**38**	**10**	NR	NR	NR
SOLO 2	**36**	**36**	**8**	NR	NR	NR
Thaci 2016	NR	NR	NR	**33**	**30**	**2**
LIBERTY AD CHRONOS	**39**	**39**	**12**	NR	NR	NR
Blauvelt 2016	NR	NA	NR	**44**	NA	**10**

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SOLO 2	36	36	8	NR	NR	NR
Thaci 2016	NR	NR	NR	33	30	2
LIBERTY AD CHRONOS	39	39	12	NR	NR	NR
Blauvelt 2016	NR	NA	NR	44	NA	10

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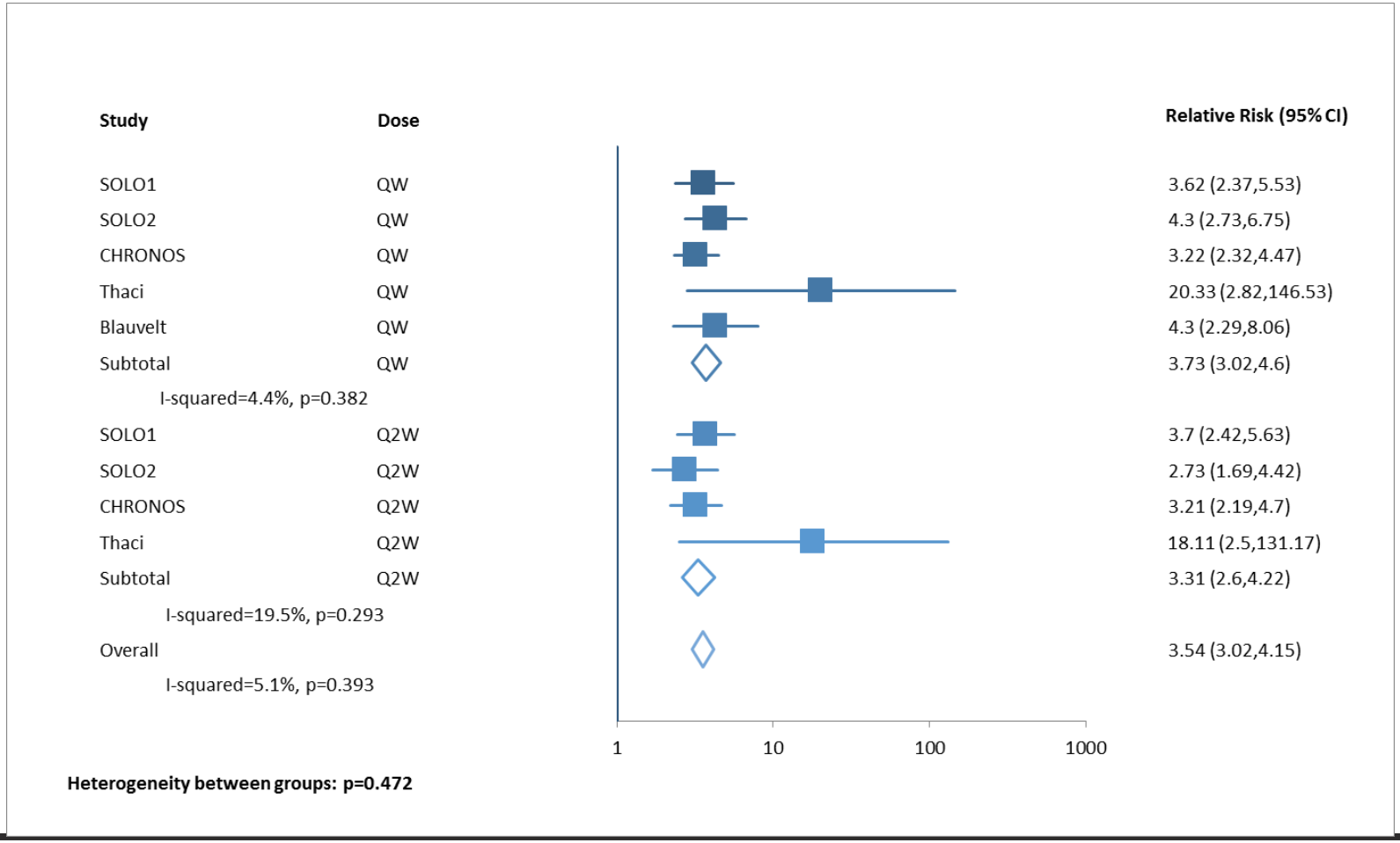
Blauvelt 2016	NR	NA	NR	**44**	NA	**10**

Forest Plot showing weekly and every other week dosing



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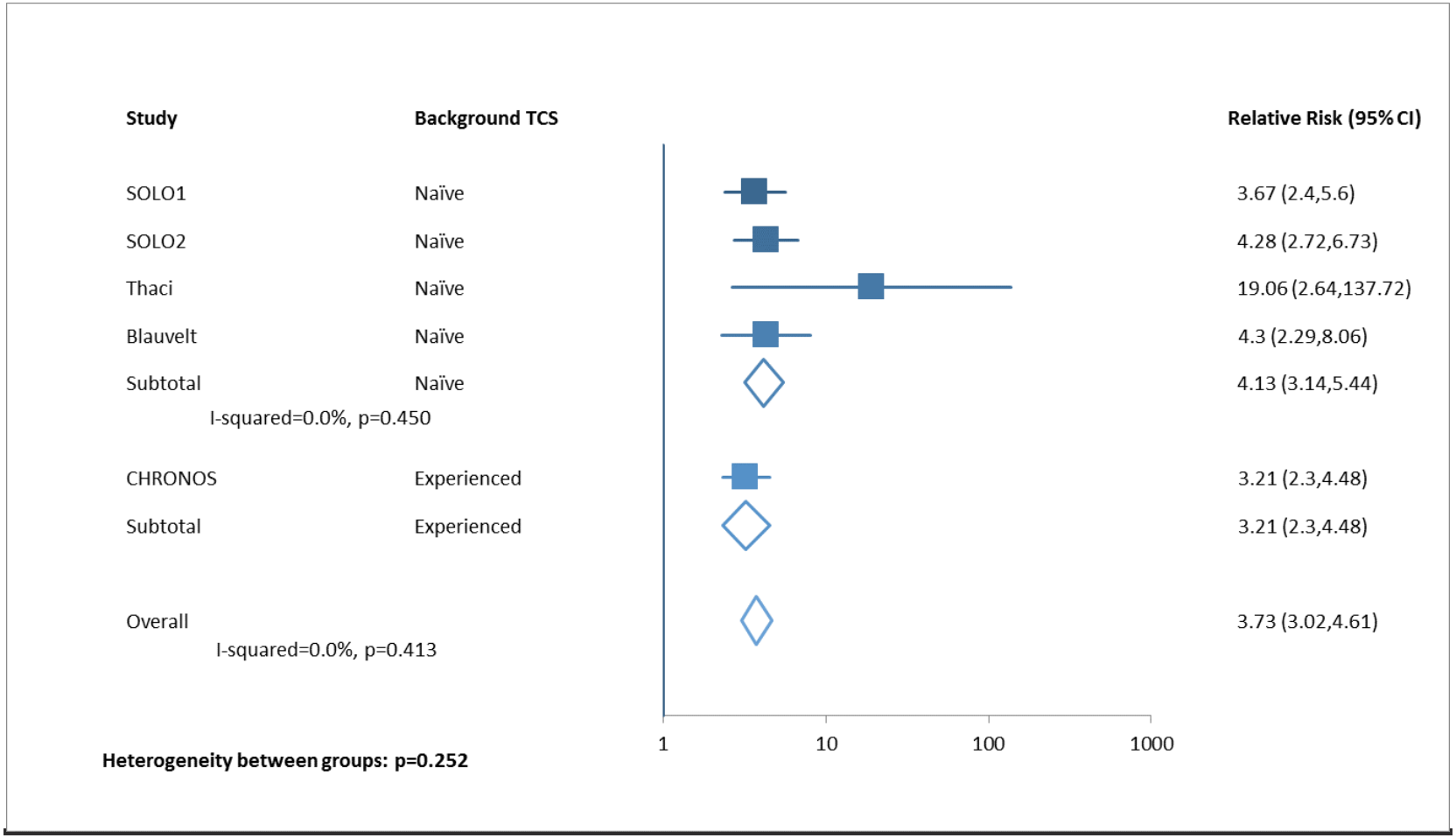
Forest plot showing background or no background topical corticosteroids



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Overall effect compared with placebo

- IGA (Investigator's Global Assessment)
  - Clear; Almost Clear; Mild; Moderate; Severe
  - Likelihood of achieving IGA of clear or almost clear (with or without ≥2 point improvement)
  - RR 3.88 (95% CI 3.13-4.79)

Overall effect compared with placebo

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  - Clear; Almost Clear; Mild; Moderate; Severe
  - Likelihood of achieving IGA of clear or almost clear (with or without ≥2 point improvement)
  - RR 3.88 (95% CI 3.13-4.79)
- EASI (Eczema Area Severity Index)
  - Assesses body surface area affected by various signs of atopic dermatitis, graded systematically
  - Likelihood of achieving a percentage improvement from baseline
  - EASI 75: RR 3.25 (95% CI 2.79-3.79)

Patient-reported Outcomes

- Quality of Life: At 16 weeks, DLQI improved 8-12 points with dupilumab vs. 1-5 points with placebo (4-point difference clinically significant)
- Itching: Reduction of 40-51% vs. 5-26%
- Reduction in anxiety and depression

Harms

- Generally infrequent and mild:
  - Injection site reactions (14% vs 7%)
  - Headaches (8% vs 5%)
  - Conjunctivitis (10% vs 4%)
- Deaths
  - Across all trials, 5 deaths among 2400 patients who received dupilumab
    - Asthma (84 days after last dose; not taking controller med)
    - Suicide (8 days after last dose; h/o severe depression)
    - Acute cardiac failure (asthma trial)
    - Metastatic gastric cancer, organizing pneumonia, cor pulmonale (asthma trial)
    - Motor vehicle accident
  - No deaths among 1121 patients who received placebo

Dupilumab versus Cyclosporine

- No direct evidence
- Systematic review found 5 RCTs comparing cyclosporine with placebo
  - Improvements of 53% to 95% in various scores
  - Trials were small, performed many years ago, used different outcome measures than current trials

Granlund 2001 RCT in 72 patients

- Cyclosporine (36) vs. phototherapy (36)
- Intermittent treatment for one year, assessed SCORAD, as did the key trials

	Baseline score*	Reduction from baseline*
Dupilumab		
SOLO 1	65	-57%
SOLO 2	68	-52%
Thaci 2016	67	-54%
Cyclosporine		
Granlund 2001	49	-55%
***For dupilumab trials, values pooled across weekly and every two week dosing groups**		

- Thus, similar reductions with cyclosporine but less severe disease at baseline

Cyclosporine harms

- Acute and chronic nephrotoxicity
- Hypertension
- Increased risks for infections and cancer

- Treatment is typically limited to one year

Phototherapy

- In Granlund 2001, cyclosporine significantly superior to phototherapy
- Based on this and other trials, dupilumab appears more effective than phototherapy

- Phototherapy can be very time consuming and may increase the risk of skin cancer

Controversies and Uncertainties

- Dupilumab is a novel therapy; we lack adequate long-term safety data
- No head-to-head trials against systemic agents
- Patients had more severe disease than the entry criteria for the RCTs (baseline EASI ≈30, required 16; baseline BSA ≈50%, required 10%)
- Efficacy and required treatment unclear over long run
- Anecdotal reports of dramatic improvements

Other Benefits or Disadvantages and Contextual Considerations

- Dupilumab is an injection given every two weeks
  - Less time-consuming than topical treatment
  - Potentially more burdensome for some patients
- Productivity effects
- Lifetime burden of illness

Dupilumab Summary

- Substantial improvements in majority of patients
- Well tolerated though increased conjunctivitis; deaths felt unrelated to treatment; important adverse effects could show up over time
- Appears to be at least as efficacious as cyclosporine, which has well-known toxicities
- Given uncertainties about safety, B+ (“Incremental or better”) versus placebo and C+ (“Comparable or better”) versus cyclosporine

Public Comments Received

- Dupilumab review should analyze moderate-to-severe as a single group
- Benefit/risk of dupilumab exceeds that of cyclosporine
- Dupilumab is superior to emollients, not incremental+
- Benefits of avoiding improper treatment with systemic corticosteroids
- Inadequate data to comment on crisaborole compared with other topicals

Cost Effectiveness

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Disclosures:

I have no conflicts of interest relevant to this report.

Objective

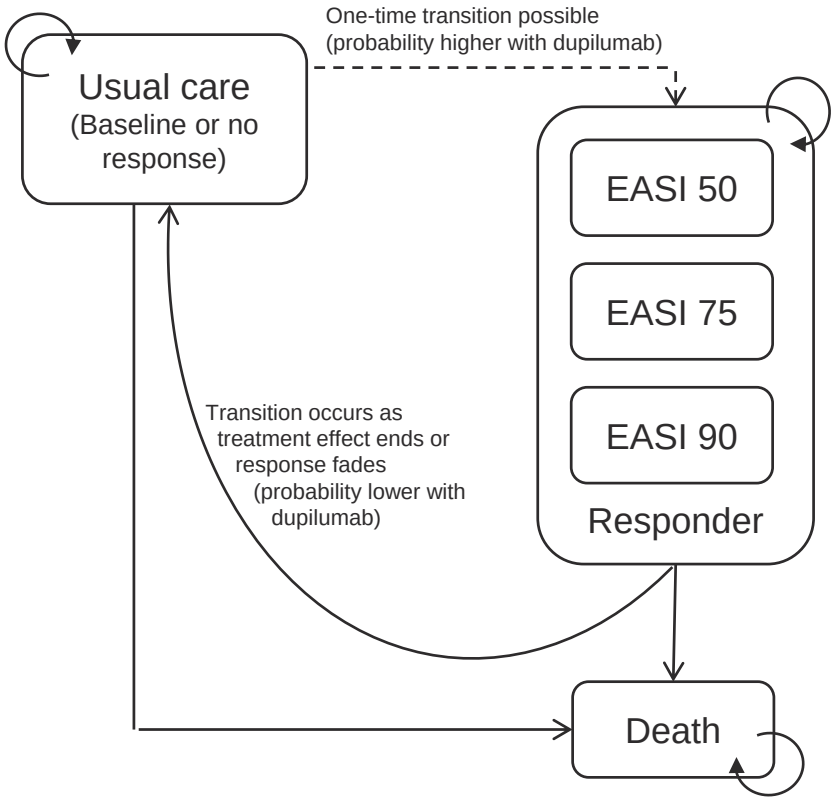
The primary aim of this analysis was to estimate the cost-effectiveness of dupilumab for moderate-to-severe atopic dermatitis compared to usual care over a lifetime horizon.

Target population: adults with atopic dermatitis who had failed topical therapy:

- Mean age of 38 years, 53% male
- 53% moderate (IGA3), 47% severe (IGA4)

Methods in Brief

Overall Approach



- Interventions:
  - Dupilumab
  - Usual care
- Modeled time in health states
  - EASI 50, EASI 75, and EASI 90
- Adjusted for quality of life (QoL) and summed over a patient's remaining lifetime

Key Model Assumptions

- Patients who transitioned to response states did so after one cycle.
- Patients did not transition between EASI 50, 75, and 90 response levels after the initial response while on treatment.
- The discontinuation rate from dupilumab was constant over time, and was equivalent for all the responder categories.
- Patients on usual care who were responders transitioned to non-response at a rate equivalent to the recurrence rate for usual care populations in the dupilumab trials.
- Atopic dermatitis disease and treatments do not affect mortality.

Clinical Inputs

- Transition to Response Categories

Baseline severity	Responder Category			Source
	EASI 50	EASI 75	EASI 90	
Moderate				
Dupilumab	16.0%	17.5%	41.0%	Sanofi-Regeneron
Usual Care	12.0%	8.3%	9.4%	Sanofi-Regeneron
Severe				
Dupilumab	24.1%	14.2%	23.3%	Sanofi-Regeneron
Usual Care	9.8%	3.9%	4.3%	Sanofi-Regeneron

- Transition to Non-Response

	Rate	Source
Dupilumab	6.3% annually	Sanofi-Regeneron data on file
Usual Care	65.8% per 16-weeks	Peserico 2008

Clinical Inputs

- Utilities

Baseline severity	Utility Value				Source
	Baseline/ no response	EASI 50	EASI 75	EASI 90	
Moderate	0.684	0.892	0.893	0.907	Sanofi-Regeneron
Severe	0.535	0.882	0.890	0.911	Sanofi-Regeneron

- Adverse Events

Adverse Event	Rate: Dupilumab	Rate: Usual care	Cost	Disutility
Injection site reaction, One-time	11.0%	--	$108.13	0.004
Allergic conjunctivitis, Per cycle	3.0%	0.9%	$73.40	0.03
Infectious conjunctivitis, Per cycle	4.3%	0.7%	$138.82	0.03

Economic Inputs

Dupilumab

- List price: $37,000[1]
- Net price: $31,000[1]
- Self-injector training: $20[2]

Other healthcare costs

- Non-responder/usual care $11,630[3]
- Responders $7,346[4]

Sources:
[1] Sanofi-Regeneron data on file
[2] 2017 physician fee schedule, CPT 99211
[3] Sanofi-Regeneron data on file, Truven Health Marketscan® Commercial Claims and Encounters database, patients with AD treated with phototherapy or any systemic immunomodulatory medications (i.e., prednisone, cyclosporine, methotrexate, azathioprine or mycophenolate) minus prescription drug costs
[4] Sanofi-Regeneron data on file, Truven Health Marketscan® Commercial Claims and Encounters database, patients with AD treated without phototherapy or any systemic immunomodulatory medications

Results

Base Case Results

	Usual Care	Dupilumab	Incremental
Results Using the List Price for Dupilumab			
Total Costs	$271,461	$509,593	$238,132
Drug Costs	--	$267,797	$267,797
Other Healthcare Costs	$271,461	$241,796	-$29,665
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$124,541
Results Using the Net Price for Dupilumab			
Total Costs	$271,461	$466,168	$194,708
Drug Costs	--	$224,372	$224,372
Other Healthcare Costs	$271,461	$241,796	-$29,665
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$101,830

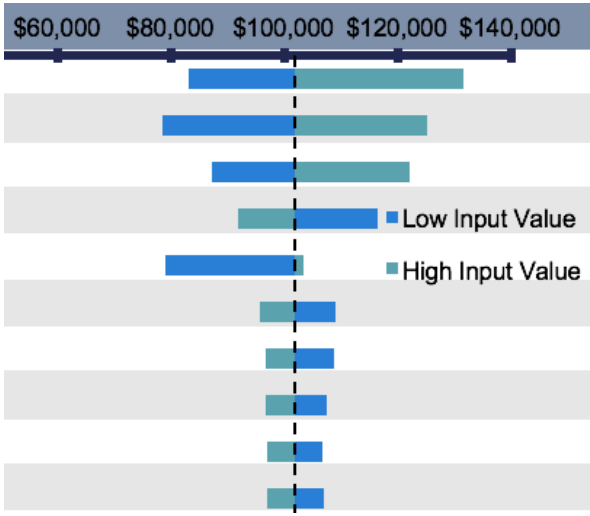
Moderate and Severe Results

	Moderate			Severe		
	Usual Care	Dupilumab*	Incremental	Usual Care	Dupilumab*	Incremental
Total Costs	$271,356	$482,861	$211,506	$271,579	$447,344	$175,765
Drug Costs	--	$243,786	$243,786	--	$202,480	$202,480
Other Healthcare Costs	$271,356	$239,075	-$32,281	$271,579	$244,864	-$26,715
QALYs	16.00	17.62	1.62	12.52	14.77	2.24
Cost per Additional QALY	--	--	$130,807	--	--	$78,295

*Using net price for dupilumab

Sensitivity Analysis

Tornado diagram* for total population

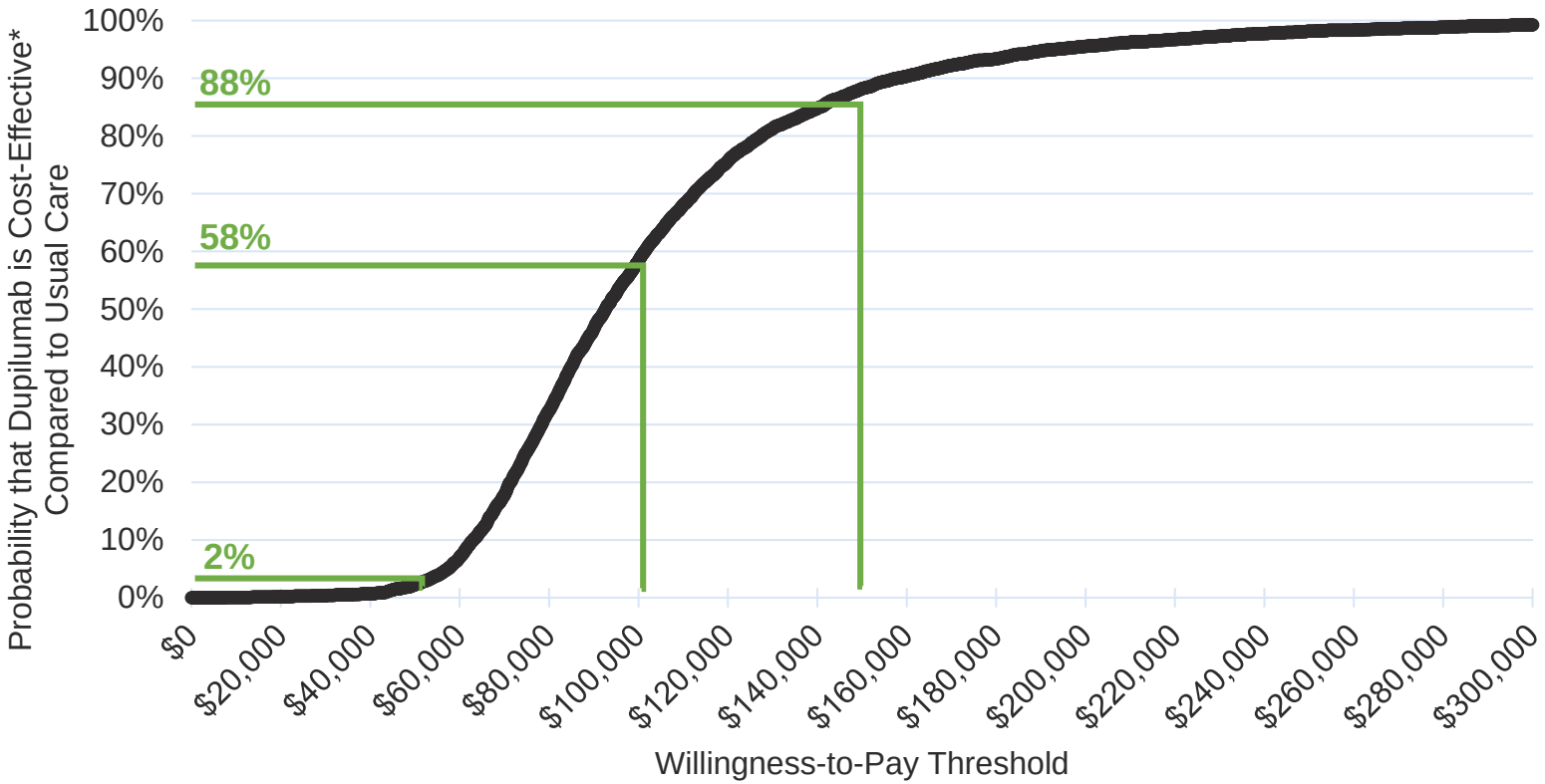


Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Dupilumab WAC	$29,600	$44,400
Utility, non-responder, severe	0.43	0.64
Utility, EASI 90, moderate	0.80	1.00
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Utility, EASI 75, moderate	0.79	1.00
Annual direct costs for moderate AD patients	$8,447	$12,671
% severe	38%	56%

*Based on net price of dupilumab

Probabilistic Sensitivity Analysis

Probability of cost-effectiveness* by willingness-to-pay (total population)



*Based on net price of dupilumab

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Limitations

- Limited data for health outcomes over long periods of time, particularly for sustained responses or discontinuation rates.
- Limited data on costs of atopic dermatitis, particularly stratified by severity.
- Atopic dermatitis is a heterogeneous condition and patients experience a wide range of symptoms and severities.

Summary

- Dupilumab improves health outcomes compared to usual care, but with additional costs.
- At the discounted price of dupilumab used in this draft report, the incremental cost-effectiveness ratio was at or below commonly cited thresholds for cost-effectiveness.
- Dupilumab was projected to be more cost-effective in patients with severe atopic dermatitis, but even in patients with moderate atopic dermatitis, the ICER remained below the upper range of commonly cited thresholds.

Comments Received

- Comorbid conditions such as asthma and infections should be included in the model.
- Results should be presented for the full population only and not stratified by severity.
- Model inputs cannot reflect a heterogeneous population.

Public Comment: Manufacturer Representatives

Public Comment

Dr. Amy Paller, International Eczema Council

Conflicts of interest:
Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

If yes please describe the relationship below:

Eli Lilly -Advisory Board
GSK/Steifel - Consultant/Advisory Board
Pierre Fabre - Advisory Board
Regeneron/Sanofi - Advisory Board

Tim Smith, National Eczema Association

Conflicts of interest:
Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

If yes please describe the relationship below:

The National Eczema Association accepts grants from pharmaceutical companies.

Corporate Partners include:

CVS Pharmacy, Lilly, Leo, Pfizer, Sanofi, Genzyme, Regeneron, Genentech, TaroPharma

Susan Lipworth, Patient

Conflicts of interest:

None to disclose

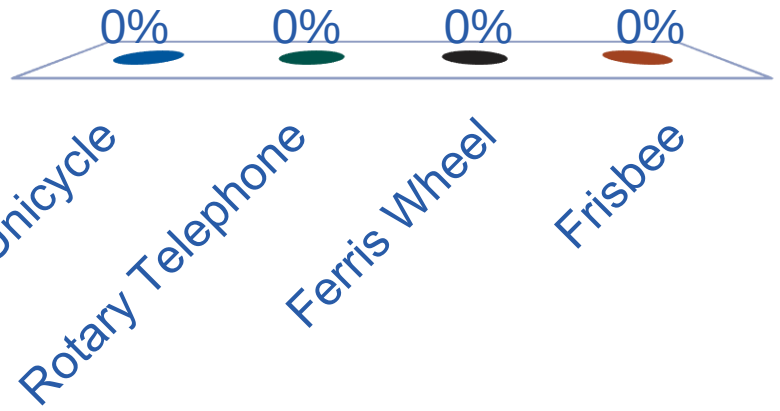
Break for Lunch

Meeting will resume at 1:00 pm

Voting Questions

0. What new invention was debuted at the 1893 Chicago World Fair?

A. Unicycle
B. Rotary Telephone
C. Ferris Wheel
D. Frisbee



1. In patients with mild-to-moderate atopic dermatitis, is the evidence adequate to demonstrate that the net health benefit of treatment with crisaborole is greater than that of treatment with topical corticosteroids or topical calcineurin inhibitors?

A. Yes

B. No

2. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that treatment with dupilumab provides additional net health benefits beyond continued non-pharmacologic treatments such as emollients?

A. Yes

B. No

3. In adults with moderate-to-severe atopic dermatitis who have failed topical therapy, is the evidence adequate to demonstrate that the net health benefit of treatment with dupilumab is greater than that of treatment with cyclosporine?

A. Yes

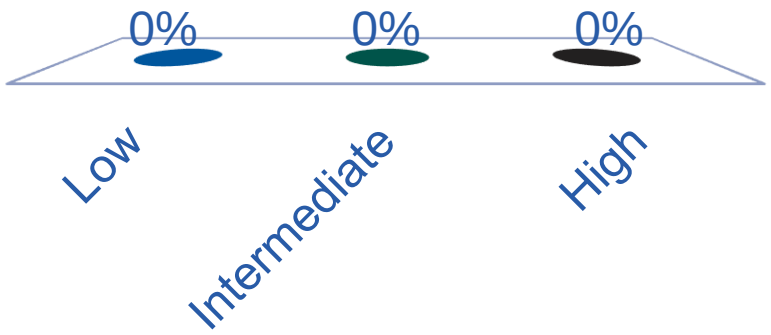
B. No

4. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in a mixed population of adults with **moderate-to-severe** atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

A. Low

B. Intermediate

C. High

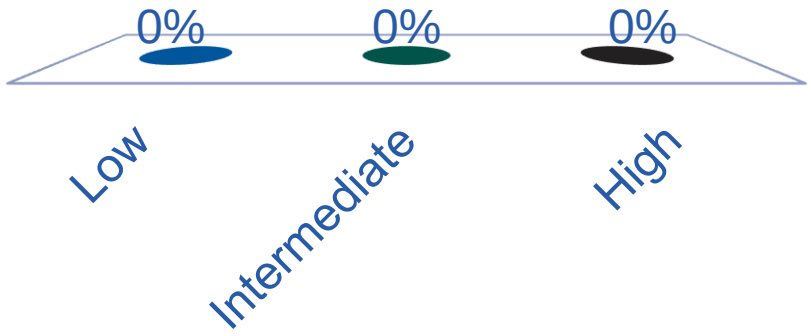


5. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with **moderate** atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

A. Low

B. Intermediate

C. High

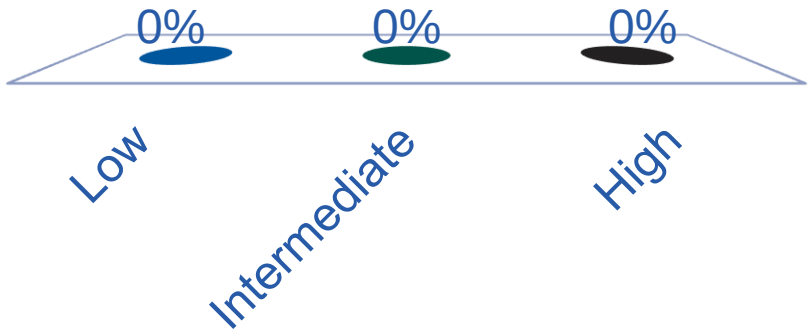


6. Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering other benefits, disadvantages, and contextual considerations, in adults with **severe** atopic dermatitis who have failed topical therapy, what is the long-term value for money of dupilumab compared with no systemic treatment?

A. Low

B. Intermediate

C. High



Policy Roundtable

Policy Roundtable Participants

Policy Roundtable	
Debbie Byrnes Patient	**David Meeker, MD** Sanofi-Genzyme
Meg Duguid Patient	**Elaine Siegfried, MD** St. Louis University
Marsha Fisher, MD Anthem Blue Cross Blue Shield Missouri	**Jonathan Silverberg, MD** Northwestern University
Jeremy Fredell Express Scripts	

Midwest CEPAC Panel Reflections

Adjourn