Validation of the Peak Pruritus Numerical Rating Scale: Results from Clinical Studies of Dupilumab in Adult Patients with Moderate-to-Severe Atopic Dermatitis

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Disclosures

- **Gil Yosipovitch:** Regeneron Pharmaceuticals, Inc. and Sanofi - Advisory Board, Honoraria
- **Matthew Reaney, Laurent Eckert, Adeline Abbe:** Sanofi - Employee, Salary and/or Stock Options
- **Vera Mastey, Marius Ardeleanu, Allen Radin, Abhijit Gadkari:** Regeneron Pharmaceuticals, Inc. - Employee, Salary, Stockholder
- **Lauren Nelson, Marci Clark:** RTI Health Solutions - Employee, Salary

Background

- Moderate-to-severe atopic dermatitis (AD) is characterized by intense, persistent, and debilitating itch (pruritus) that has a demonstrated, profound negative impact on patients' lives;[1] hence, reducing itch is an important treatment goal[2,3]
- In the absence of fully validated scales to assess itch,[4] the Peak Pruritus Numerical Rating Scale (NRS) was developed to provide a robust measurement of patient-reported itch intensity in moderate-to-severe AD
- Peak Pruritus NRS:
  "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"
- The item was completed daily via an Interactive Voice Response System (IVRS) from baseline through Week 16 in:
  - A randomized, placebo-controlled, parallel-group, dose-ranging phase 2b clinical study; and
  - Two identically designed randomized, double-blind, placebo-controlled, parallel-group phase 3 studies (SOLO 1 & 2) of dupilumab conducted in adults with moderate-to-severe AD

1. Simpson EL, et al. J Am Acad Dermatol. 2016;74:491-8. 2. Murota H, et al. Eur J Dermatol. 2010;20:410-1.
3. Sutton EL, et al. Med Clin North Am. 2014;98:1123-43. 4. Ständer S et al. Acta Derm Venereol. 2013;93:509-14.

Objectives

- To conduct content validation and psychometric assessment of the Peak Pruritus NRS
- To demonstrate that the Peak Pruritus NRS is a well-defined and reliable patient-reported outcome (PRO) measure for evaluating itch intensity in the context of clinical trials among moderate-to-severe AD patients

Methods

Content Validation

- Consistent with the principles outlined in the Food and Drug Administration (FDA) PRO Guidance for Industry,[1] content validation for the Peak Pruritus NRS was performed through in-depth patient interviews
- In line with published recommendations for cognitive testing, interviews were conducted with 14 adults with AD.[2]
  - Two geographic locations: Detroit, Michigan (n = 6), and Tampa, Florida (n = 8)
  - Participants were required to have AD for ≥ 3 years and self-reported moderate-to-severe itch
  - Each one-on-one interview was conducted in English by the same pair of experienced interviewers who followed a semi-structured interview guide

1. Food and Drug Administration. 2009. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM193282.pdf. Accessed June 21, 2016. 2. Patrick DL, et al. Value Health. 2011;14:978-88.

Methods

Psychometric Assessment

- Exploratory and confirmatory psychometric assessments were conducted using data from two sources:
  - **Exploratory analysis:** A randomized, double-blind, placebo-controlled, parallel-group, dose-ranging phase 2b clinical study; primary endpoint at 16 weeks (NCT01859988)
  - **Confirmatory analysis:** Pooled data from two identically designed , randomized, double-blind, placebo-controlled, parallel-group phase 3 studies (SOLO 1 & 2; NCT02277743, NCT02277769) of dupilumab in adults with moderate-to-severe AD; primary endpoint at 16 weeks
- Detailed study design as well as efficacy and safety results for the phase 2b study[1] and for the two phase 3 studies[2] have been published previously
- The analysis population in all studies consisted of all randomized patients who received at least one dose of dupilumab or placebo and had at least one post-baseline Peak Pruritus NRS assessment during the treatment period

1. Thaçi D, et al. Lancet. 2016;387:40-52. 2. Simpson EL, et al. N Engl J Med. 2016; 375:2335-2348.

Methods

Psychometric Assessment

- Psychometric evaluation included assessment of:
  - Cross-sectional measurement properties
    - **Construct validity:** To demonstrate stronger relationships among measures addressing similar constructs (convergent validity) compared with measures addressing more disparate constructs (divergent validity)
    - **Known-groups validity:** To compare various subgroups of interest (extreme bands in Dermatology Life Quality Index [DLQI] itch item and Patient Global Assessment of Disease [PGAD]) that are hypothesized to have different scores on the Peak Pruritus NRS
  - Longitudinal measurement properties
    - **Test-retest reliability:** To provide an evaluation of reliability by comparing scores in the measured construct across two time periods of no anticipated change
    - **Sensitivity to change**: To demonstrate the sensitivity of Peak Pruritus NRS to an expected change

Methods

Psychometric Assessment

Measures Relevant to the *Cross-sectional* Psychometric Evaluations

Outcome Measure	Response Scale	Recall Period	Analysis
Construct validity			
Average Pruritus NRS	11-point scale: 0 to 10	24 hours	Correlational analysis between the Peak Pruritus NRS scores and scores on each outcome measure at BL confirming a priori hypotheses
SCORAD itch VAS	Range: 0 to 10	Current	
DLQI itch item	4-point scale: 0 (not at all) to 3 (very much)	Past week	
PCS	4-point scale: 0 (absence of pruritus) to 3 (severe pruritus)	24 hours	
EASI	Range: 0 to 72 points	Current	
IGA	5-point scale: 0 (clear) to 4 (severe)	Current	
Known-groups validity			
DLQI bands (no impact, extremely large impact)	Range: 0 to 30 points	Current	Known-groups ANOVA at Week 16 comparing mean Peak Pruritus NRS scores confirming a priori hypotheses
PGAD (excellent, poor)	5-point scale: 1 (poor) to 5 (excellent)	Current	

ANOVA, analysis of variance; BL, baseline; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PCS, Pruritus Categorical Scale; SCORAD, SCORing Atopic Dermatitis; VAS, visual analog scale.

Methods

Psychometric Assessment

Measures Relevant to the *Longitudinal* Psychometric Evaluations

Outcome Measure	Response Scale	Recall Period	Analysis
Sensitivity to change			
SCORAD itch VAS	Range: 0 to 10	Current	Correlation analysis between the change in Peak Pruritus NRS (BL to Week 16) and the change in each outcome measure
DLQI itch item	4-point scale: 0 (not at all) to 3 (very much)	Past week	
PCS	4-point scale: 0 (absence of pruritus) to 3 (severe pruritus)	24 hours	
EASI	Range: 0 to 72 points	Current	
IGA	5-point scale: 0 (clear) to 4 (severe)	Current	

Results

Patient Characteristics

- Patient characteristics were similar between the phase 2b and pooled phase 3 study participants

Variable	Content validation	Psychometric assessment	
	Cognitive Interviews (N=14)	Phase 2b (N=379)	Pooled Phase 3 (N=1,379)
Female, n (%)	9 (64.3)	145 (38.3)	581 (42.1)
Age, mean (SD)	40.1 (15.2)	37.0 (12.2)	38.3 (14.3)
Race, n (%)			
White	7 (50.0)	257 (67.8)	939 (68.9)
African-American	4 (28.6)	33 (8.7)	94 (6.9)
Asian	0	82 (21.6)	300 (22.0)
Ethnicity, Hispanic or Latino, n (%)	3 (21.4)	14 (3.7)	52 (3.9)
Body Mass Index (kg/m^2), mean (SD)	-	26.2 (6.1)	26.5 (5.7)
Duration of AD, mean (SD)	-	28.0 (13.6)	28.1 (15.0)

SD, standard deviation.

Results

Content Validation

- All participants reported itching as a symptom of their AD
- Interpretation of the Peak Pruritus NRS was precise and consistent across participants
- Participants indicated that the Peak Pruritus NRS item was relevant to individuals with AD, was clear and easy to answer, and comprehensive in its assessment of itch severity
- Thus, the results presented here provide support for the content validity of the Peak Pruritus NRS

Results

Psychometric Assessment: Construct Validity

- The patterns of the baseline correlations between the Peak Pruritus NRS and the SCORAD itch VAS, DLQI itch item, and PCS were in the anticipated direction and strong in magnitude
- Correlations with dissimilar constructs (EASI and IGA) were expectedly weak-to-moderate

	Pearson Correlation Coefficient with Peak Pruritus NRS (r)	
	Phase 2b (N=369)	Pooled Phase 3 (N=1,373)
PRO Measures		
Average Pruritus NRS	1.00	0.92[a]
SCORAD Itch VAS	0.77	0.72[b]
DLQI Itch Item	0.67	0.61
PCS	0.75	0.66[a]
ClinRO Measures		
EASI	0.09	0.21
IGA	0.17	0.24

[a] n=1,374. [b] n=1,363.
ClinRO, clinician-reported outcome.

Results

Psychometric Assessment: Known-Groups Validity

- In terms of discriminating ability, the Peak Pruritus NRS differed predictably and significantly across known groups based on the PGAD and the DLQI score bands
- Furthermore, large effect sizes were shown for the differences between extreme categories for each known-group comparison

	Peak Pruritus NRS Score, Mean (SD) at Week 16	
	Phase 2b (N=379)	**Pooled Phase 3 (N=1,379)**
PRO Measures		
DLQI Itch Item bands		
no impact	1.84 (1.4)	2.06 (1.8)
extremely large impact	7.63 (2.0)*	7.51 (1.9)*
PGAD		
excellent	2.10 (1.9)	1.61 (1.6)
poor	5.97 (2.3)*	6.60 (2.2)*

* $P < 0.0001$ for extremely large impact vs no impact or poor vs excellent.

Results

Psychometric Assessment: Test-Retest Reliability

- The Peak Pruritus NRS yielded high test-retest reliability coefficients; intra-class correlation coefficients (ICCs) were 0.95 or higher for the test-retest evaluations using phase 2b and phase 3 data, well above the recommended 0.70 threshold for multi-item tools[1]

	Phase 2b (N=323)	Pooled Phase 3 (N=1,275)
Peak Pruritus NRS ICC (95% CI) at Week 15 Test and Week 16 Retest	0.95 (0.94, 0.96)	0.96 (0.95, 0.96)

CI, confidence interval.

1. Nunnally J and Bernstein I. Psychometric Theory. 3rd ed. New York: McGraw Hill; 1994.

Results

Psychometric Assessment: Sensitivity to Change

- The Peak Pruritus NRS demonstrated exceptional responsiveness based on the strong correlations of change observed with the PRO and ClinRO measures

	Pearson Correlation Coefficient with Peak Pruritus NRS Change from Baseline, r (n)	
	Phase 2b (N=379)	**Pooled Phase 3 (N=1,379)**
PRO Measures		
SCORAD Itch VAS	0.77 (n=320)	0.73 (n=1,259)
DLQI Itch Item	0.66 (n=320)	0.64 (n=1,273)
PCS	0.71 (n=321)	0.72 (n=1,280)
ClinRO Measures		
EASI	0.50 (n=321)	0.46 (n=1,273)
IGA	0.50 (n=321)	0.46 (n=1,273)

Conclusions

- The qualitative research study supports the content validity (appropriateness of concept, consistent comprehension of instrument, simplicity of response) of the Peak Pruritus NRS
- The phase 2b analytic results indicate that the Peak Pruritus NRS is reliable, demonstrates strong construct validity and discriminating ability, and is able to detect change
- The pooled phase 3 monotherapy trial results provide solid confirmation of the measurement properties computed using the phase 2b data
- Taken together with the evidence supporting its content validity, these quantitative results suggest that the Peak Pruritus NRS is a fit-for-purpose, well-defined, and reliable measure to evaluate peak pruritus intensity in the context of a clinical trial among patients with moderate-to-severe AD

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- ClinicalTrials.gov Identifiers: NCT01859988, NCT02277743, NCT02277769.
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Summary Slides for Oral Presentation

Validation of the Peak Pruritus Numerical Rating Scale: Results from Clinical Studies of Dupilumab in Adult Patients with Moderate-to-Severe Atopic Dermatitis

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Background and Objectives

- **Background:**
  - Itch (pruritus) has a profound negative impact on the lives of moderate-to-severe atopic dermatitis (AD) patients[1]; hence, reducing itch is an important treatment goal in these patients[2,3]
  - Peak Pruritus Numerical Rating Scale (NRS) was developed as a single, self-completed item that assesses the intensity of peak (worst) pruritus during the past 24 hours:

    "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"

- **Objectives:**
  - To conduct content validation and psychometric assessment of the Peak Pruritus NRS
  - To demonstrate that the Peak Pruritus NRS is a well-defined and reliable patient-reported outcome (PRO) measure for evaluating itch intensity in the context of clinical trials among moderate-severe AD patients

1. Simpson EL, et al. J Am Acad Dermatol. 2016;74:491-8. 2. Murota H, et al. Eur J Dermatol. 2010;20:410-1. 3. Sutton EL et al. Med Clin North Am. 2014;98:1123-43

Methods

- **Content validation** was performed through in-depth patient interviews as recommended by the Food and Drug Administration (FDA)[1]
- **Psychometric assessment** was conducted using data from 2 separate sources:
  - a randomized, placebo-controlled, phase 2b study for *exploratory analysis* [2]
  - pooled data from 2 identically designed , randomized, placebo-controlled, phase 3 studies for *confirmatory analysis* [3]
  - The analysis population in all studies was all randomized patients who received at least one dose of dupilumab or placebo and had at least one post-baseline Peak Pruritus NRS assessment during the treatment period
- Specific psychometric assessments included:
  - *Construct validity*: To demonstrate stronger correlations among measures addressing similar constructs (convergent validity compared with measures addressing more disparate constructs (divergent validity)
  - *Known-groups validity*: To compare various subgroups of interest that are hypothesized to have different scores on the Peak Pruritus NRS.
  - *Test-retest reliability*: To provide an evaluation of reliability by comparing scores in the measured construct across two time periods of no anticipated change
  - *Sensitivity to change*: To demonstrate the sensitivity of Peak Pruritus NRS to an expected change in SCORing Atopic Dermatitis (SCORAD) itch Visual Analogue Scale (VAS), Dermatology Life Quality Index (DLQI) itch item, Pruritus Categorical Scale (PCS), Eczema Area and Severity Index (EASI), and Investigator's Global Assessment (IGA)

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