Nocturnal Scratch in Atopic Dermatitis

Advancements in Digital Measurement & Regulatory Qualification

Objectives

A collaborative study to advance the regulatory qualification of digital measurement solutions [2023-24]:

1. **DEEP Measures**
2. **European Federation of Pharmaceutical Industries and Associations (EFPIA)**
3. **European Medicines Agency (EMA)**

Purpose: Explore the application of DEEP concepts, utilizing an extended Innovation Task Force (ITF) procedure, to inform the optimization of the Qualification of Novel Methodologies procedure.

Ultimate Goal: Establish nocturnal scratch as a digital endpoint for atopic dermatitis.

Methods

A multi-stakeholder consortium, including 7 top pharma companies, built upon prior work under the Digital Medicine Society (DiMe) framework to seek regulatory advice on three key aspects:

1. Defining nocturnal scratch as a measurable concept.
2. Validating digital measurement solutions using a standardized technology framework.
3. Assessing transferability of evidence from atopic dermatitis to psoriasis.

Results

EMA Feedback was received on six areas:

1. **Conceptual Model** – Establishing a framework for using nocturnal scratch as a digital endpoint.
2. **Terminologies & Ontologies** – Defining standardized language and classification for the measure.
3. **Context of Use & Clinical Meaningfulness** – Evaluating the endpoint's relevance and impact in clinical settings.
4. **Evidence for Development & Validation** – Reviewing data supporting the endpoint's accuracy and reliability.
5. **Validation Steps & Requirements** – Defining the necessary steps to refine or modify the endpoint.
6. **Adaptation for Different Diseases or Instruments** – Determining how the endpoint can be extended to other conditions or measurement tools.

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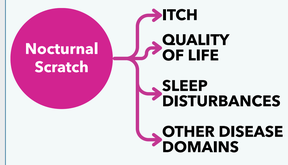
Conclusions: This work represents a significant step toward the regulatory acceptance of digital health technologies in dermatology, potentially improving disease monitoring and patient outcomes.

Conceptual Model for Nocturnal Scratch

The EMA ITF agreed that nocturnal scratch is:

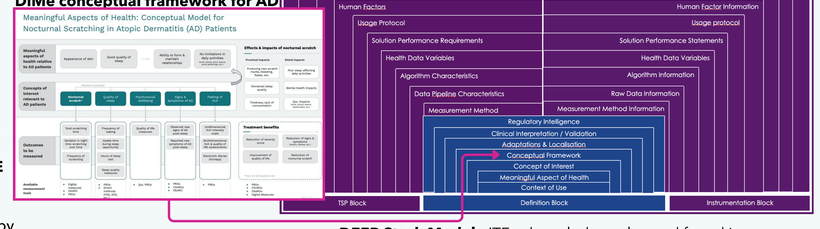
- A **symptom** of Atopic Dermatitis (AD)
- A **valuable component** of the disease to target as an individual endpoint
- An element that **adds additional value** alongside existing endpoints

Consideration:
Key interrelationships



These may not be fully elucidated by the DiMe study alone.

DiMe conceptual framework for AD



Future Expectations:

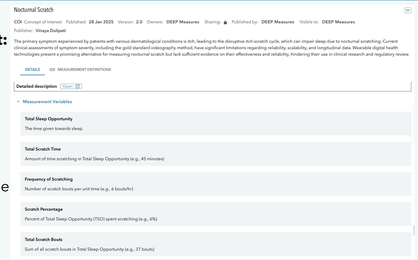
1. Future studies should provide quantitative evidence on the relationship between nocturnal scratch and other disease domains.
2. This evidence should be included as part of the clinical validation package.

DEEP Stack Model - ITF acknowledge value and found it was helpful to 're-use' data for future adaptations

Terminologies & Ontologies

The ITF could envisage a more appropriate term, but:

- They are currently willing to accept "nocturnal scratch".
- The term has been used in the scientific literature for quite a while.
- It describes the majority of the population, with the realization that there would be additional context provided by the sponsor.



Nocturnal scratch as a secondary endpoint for pediatric and adult patients with mild to severe Atopic Dermatitis.

Target Population:
Age Range - patients aged 2 years and older
Disease severity - Patients with mild to severe Atopic Dermatitis

Setting
The digital measure is intended for use in the home setting to capture real-world nocturnal scratching behavior.

Overall purpose
This digital measure is intended for use in clinical trials as a secondary endpoint to assess the efficacy of therapeutic interventions in reducing nocturnal scratching in patients with AD.

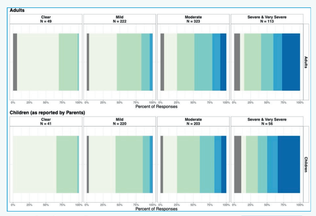
Context of Use & Clinical Meaningfulness

Context of Use (CoU)
Nocturnal Scratch as a secondary endpoint to measure efficacy of treatments for AD in pivotal confirmatory clinical trials for mild to severe AD patients, 2 years and older.

ITF Feedback
ITF backed the potential and agreed with the proposed CoU, subject to:

- Additional detail needed for individual use cases
- Demonstrating the ability to detect change
- Characterizing the Minimal Clinically Important Difference (MCID)

Meaningful Aspect of Health (MAH) to Patients and Relationship to Disease



Results from Survey:
"During the past two weeks, how often did you [observe your child] scratch at night because of your [their] eczema?"

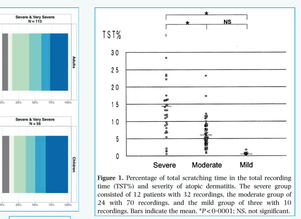


Figure 1. Percentage of total scratching time in the total recording time (TST%) and severity of atopic dermatitis. The severe group consisted of 12 patients with 32 recordings, the moderate group of 24 with 70 recordings, and the mild group of three with 10 recordings. Bars indicate the mean. *P<0·0001: NS, not significant.

Figure from: Ebata T, Aizawa H, Kamide R, Niimura M. The characteristics of nocturnal scratching in adults with atopic dermatitis. Br J Dermatol. 1999;141(1):82-86. doi:10.1046/j.1365-2133.1999.02924.x

Future Expectations:
The sponsor would be required to:

- Provide appropriate justification for their specific CoU
- Address additional evidentiary requirements, including:
  - Clinical meaningfulness of the measure
  - Benefit if used as a primary or secondary endpoint

"As the severity of AD increased, there was an increased bothersomeness, intensity, and frequency observed in all surveyed symptoms and effects."
– Cesnakova et al., 2023

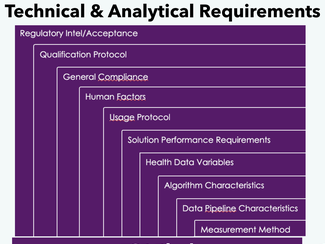
Evidence for Development & Validation

Body of Evidence Needed for Regulatory Validation of Nocturnal Scratch Measure in AD

- ITF had no overarching concerns with the strategy proposed.
- The discussion centered on:
  - Use of natural history studies
  - Derivation of MCID
- ITF acknowledged:
  - AD is not a progressive disease, but rather one that is in flux and prone to flares
  - Analytical validation with patient coefficients of variation would cover variability related to flares
- ITF were open to alternative & complementary methods to determine MCID, however, they noted that additional detail, context, and discussion would be required.

Standardization of DHT Requirements Through TSP

Technical & Analytical Requirements



Target Solution Profile (TSP):
Accelerometry-based measurements of Nocturnal Scratch

-->A set of features and **quirements** that define the **standard** for the wrist-worn-accelerometry-based measurement of Nocturnal Scratch, classified into essential and desirable based on their importance.

DEEP-EMA-EFPIA Pilot: Qualification of Novel Methodologies (QoNM)

DEEP (J&J, Novartis, Roche, Bayer) & EFPIA Team (efpia DEEP) → Planning and organizing the pilot → **EMA & EMRN Team** → ITF Procedure as a pilot environment → **Applicant Team: Sanofi, Abbvie, UCB, Lilly, Pfizer, J&J, Novartis, GSK**

Collaboration - Enhanced pre-competitive collaboration and involvement of relevant experts

Standards - Standardized model and re-use of evidence for novel methodologies validation

Lifecycle Management - Lifecycle management components

Knowledge Management - Enabling more targeted, specific regulatory feedback

Accelerate Adoption - Dynamic regulatory advice on digital measures

Pilot Tested Optimization of QoNM Procedure

Feedback from EMA, Assessors and Pharma

"Re-using structured evidence to extend to new conditions showed large potential"

"Focus on Technology agnostic digital endpoint development was appealing to participants"

"Structured approach has the potential to increase the quality of evidence submitted"

"Pilot on a real use case provided (a lot of) true user feedback for further development"

Adaptation for Different Diseases or Instruments

Evidence requirements for the addition of a New Definition Block: Psoriasis

- ITF noted - There may need to be bridging data/comparability studies for new conditions.
- In psoriasis specifically:
  - Different anatomical locations and scratching patterns may be observed.
  - Within-patient coefficient of variation would be valuable to capture.

Conclusion: While the concept is valuable, bridging studies would offer reassurance of validation and will likely be needed.

Requirements for adding a New Instrumentation Block: Hardware and/or Algorithm

The ITF expressed positivity in the large potential for the described paradigm.

- If a link between observed variability in analytical validation and technical performance characteristics is demonstrated, then bench testing may be sufficient.
- For more significant changes, such as using a different DHT type to measure the same aspect of health, additional validation may be required
  - This level of rigor is considered desirable

Proposed Pathway to Develop and Validate the Selected Digital Measures as a Secondary Endpoint in a Clinical Trial

Study	Activity	Objective	Summary	Summary (for Psoriasis)*	Summary (New Hardware/ Algorithm)	Requirement (for Psoriasis)*	Requirement (Hardware Change)	Requirement (Algorithm Change)
Qualitative study	Concept elicitation	Establish nocturnal scratch as an important concept that matters to AD patients	Structured interviews with patients and their partners, further supported by survey data from patients and caregivers.			Required	No Additional Evidence Required**	No Additional Evidence Required**
Feasibility & Analytical validation study (non-therapeutic) - evidence may be available from DHT manufacturers	DHT Feasibility	Demonstrate patient feasibility of deploying DHT to collect data in patients with AD	- Patient feedback on the use of the DHT - Evaluate compliance - Understand barriers and facilitators for patients, for example through a structured questionnaire, to enable optimum deployment in future studies			No additional evidence required as population has similar characteristics	Supplemental Evidence Required***	
		Demonstrate operational feasibility of deploying DHT to collect data in patients with AD	- Clinical site feedback on the use of the DHT - Identify operational issues arising from DHT deployment (e.g., technical issues, DHT-related adverse events (AEs) - Understand operational barriers and facilitators, for example through a structured questionnaire, to enable optimum deployment in future studies					
	Analytical Validation	Assess the performance of DHT in measuring nocturnal scratch (duration, number of events) in patients with AD	Comparison to gold standard measure, e.g., videography and polysomnography				Supplemental Evidence Required***	Supplemental Evidence Required***
		Evaluate the reliability of DHT-derived nocturnal scratch measures	Within-patient coefficient of variation of nocturnal scratch measures over various periods of time					
Therapeutic study(/ies)	Analytical Validation	Evaluate the sensitivity to change of DHT-derived nocturnal scratch measures	Explore changes over time (e.g., relative rate of change over time)					
	Clinical Validation	Evaluate correlations between proposed measures and other clinical outcomes	Correlation of DHT-derived nocturnal scratch measures with clinical and other measures of disease severity and efficacy assessments:			Required	No Additional Evidence Required**	No Additional Evidence Required**
			i.e. PROs (e.g., NRS Itch), Skin lesions, Primary/secondary efficacy assessments, e.g., EASI, SCORAD or VIGA-AD	i.e. PROs, Primary/secondary efficacy assessments, e.g., IGA, PASI 20/50	i.e. PROs, Skin lesions			
	Minimal Meaningful Change	Define minimum meaningful change that can be interpreted as treatment benefit	Anchor-based methodology (e.g., using PGI-S as an anchor) as well as distribution-based methods as supportive.					
			Literature supporting the meaningful changes observed in standard sleep and scratch/lesion measures					

* Replace AD in Objective wherever applicable with Psoriasis.
** No additional evidence is required if the new instrument meets the previously qualified TSP and demonstrates equivalence to previously used instrument.
*** Supplemental evidence equates bridging or additional supporting studies to support the change.