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ITF Briefing Meeting report

DEEP

ITF Briefing meeting held virtually with the European Medicines Agency (EMA) on 17/01/2024.

The objective of the ITF Briefing Meetings is to provide for a preparatory discussion on scientific and regulatory topics relevant to the development of new medicinal products and technologies complementing and reinforcing existing formal procedures.

Name/identifier:	[redacted]
Product / technology / method / methodology description:	Digital Evidence Ecosystem and Protocols (DEEP) initiative using the example of measurement of nocturnal scratch in atopic dermatitis
Intended use:	(1) To discuss the advancement of digital nocturnal scratch as a measure for use in clinical trials of therapeutic interventions in atopic dermatitis. (2) To enable pre-competitive and multi-stakeholder collaboration, facilitate an ecosystem of services to connect stakeholders and a catalogue that enables re-use of aspects of the digital measure solutions.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Un on

Participants

Applicants:

Number	First name	Surname	Role
[redacted]			

EMA experts:

First name	Surname	Organisational entity
[redacted]		

External experts:

First name	Surname	Committee or Working Party	Country	NCA
[redacted]				

Disclaimer presented at beginning of meeting

The views expressed in this document are the opinion of the participating members of the Innovation Task Force and the experts and may not reflect the opinion of the EMA scientific committees. Therefore, the answers provided should not be interpreted as regulatory guidance or review recommendations for an application, but as a preliminary set of scientific considerations of the information presented.

Should aspects of the subject matter discussed herein become part of a formal data submission, application, or supplement, it is at the full discretion of the appropriate working party, evaluation team or scientific committee to completely and independently assess the product(s)/technology(ies) in question.

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1. Background

The purpose of the meeting with the European Medicines Agency (EMA) was to discuss the advancement of a digital nocturnal scratch as a measure for use in clinical trials of therapeutic interventions in atopic dermatitis. With the ultimate goal being that in the future these measures can be used as primary and/or secondary endpoints within clinical trials as a sponsor would require. This meeting utilized the DEEP platform for information sharing with the Agency and therefore this engagement also serves as a proof of concept for the use of the DEEP platform for multi-stakeholder interactions with a health authority. This is a pre-competitive collaboration between industry consortium with representation from DEEP, Pfizer, Janssen, GSK, Eli Lily, UCB, Abbvie, Novartis, and Sanofi. The consortium developed six questions and accompanying positions for EMA ITF feedback, specifically addressing:

- The conceptual model for a digital nocturnal scratch endpoint in AD clinical trials
- The terminologies and ontologies for a nocturnal scratch endpoint/measure
- The context of use and clinical meaningfulness of a nocturnal scratch endpoint
- The evidence for development and validation of a nocturnal scratch endpoint
- The validation steps/requirements needed to change/modify/add a building block within the solution. Specifically change the disease and/or the instrumentation

The Digital Evidence Ecosystem and Protocols (DEEP) initiative was developed to assist with digital endpoint development ecosystem. The solution consists of collaboration ecosystem that enables pre-competitive and multi-stakeholder collaboration, an ecosystem of services to connect relevant stakeholders and facilitate those connections, and a catalogue (stack) that enables re-use of aspects of the digital measure solution. The DEEP stack model presents information specific to digital measure in the structure of 3 building "blocks". These 3 blocks are interrelated: the Measurement Definition block, the Target Solution Profile (TSP) block and the Instrumentation block. We used this DEEP model and developed and presented the novel digital measure of nocturnal scratch, specific to the context of use of atopic dermatitis as an example of how it may be utilized moving forward. With questions being presented specific to that measure and in relation to the blocks presented.

The first series of questions (Q 1, 2, 3) presented encompassed the measurement definition block, specifically, the nocturnal scratch conceptual model (specific to the COI) and patient meaningfulness of the measure, Terminology and Ontology and the Context of Use (COU). Question 4 specifically addressed the validation/testing paradigms of the entire digital measurement solution. Using the building blocks, Question 5 focused on changing the disease area while maintaining the TSP and instrumentation block and Question 6 focused on changing the instrumentation block while maintaining the TSP and COU. The blocks that have been created were developed from published studies and literature specific to nocturnal scratch. In the future, as Applicants consider using this measure in their specific programs, these existing blocks may be supplemented with applicant-specific additional information.

2. Topics discussed

Introductory remarks

ITF members were happy to discuss scientific ideas, but all opinions should be considered as personal and not representative of committee opinions (e.g., CHMP or SAWP).

There will be no written letter as an outcome and draft minutes due from the Applicant by 31 Jan 2024 which will be commented and serve as a meeting record.

In the light of the information provided and the discussion held, key points outlined by the experts and Applicant are summarised after each topic and/or sub-topic in the sections below.

Topic 1: Conceptual Model for Nocturnal Scratch

Applicant Question 1: Does the Agency agree with the proposed conceptual model for nocturnal scratch and relationship between nocturnal scratch and meaningful aspects of health (MAH) for patients affected by atopic dermatitis (AD) and their care partners?

Applicant's Position

The applicants, literature and surveys illustrate that nocturnal scratch is a symptom of atopic dermatitis (AD) and that this is a meaningful aspect of health for the patients, and their caregivers.

AD also known as atopic eczema, is a chronic inflammatory skin disease affecting both adults and children. The features of AD include skin redness, thickness and lichenification, as well as the most common symptom with the greatest reported disease burden in AD patients – itch. It is a complex and subjective "sensation", often accompanied by the physical action (movement) of scratching. Scratching further aggravates dermatitis leading to a further itch sensation and consequent urge to scratch. This has been coined as the itch-scratch-cycle in AD. The terms of "itch" and "scratch" are often used interchangeably when discussed; however, they are and thus should be recognized as two independent, but interrelated, symptoms that are encountered by patients with AD. It must also be noted while itch and scratching can be related, one may scratch without the itch sensation, or feel the itch sensation and not scratch. Scratching damages the epidermal skin barrier, including damaging the outer skin layer, leading to allergen and bacterial infiltration, inflammatory and immune responses, downstream signalling and stimulation of itch sensory neurons. Itch and scratching behaviours have been associated with significant negative effects on patients' mood, sleep, functioning, worsening of AD symptoms and overall quality of life. Patients with AD may wake up repeatedly during the night to scratch due to the excessive itchiness, and the repeated waking and loss of sleep is one of the most distressing impacts of AD on patient's living with the condition, as well as their family members or other caregivers.

ITF Discussion – Key Points on Topic 1

Overall, the EMA ITF agreed that nocturnal scratch was a symptom of AD as well a valuable component of the disease to be targeted as an individual endpoint. In addition, these measures would add value in concert with existing endpoints. Questions were raised around the interrelationships between nocturnal scratch and itch, sleep disturbances, quality of life, and other domains of the disease which may not be fully elucidated by the DiMe study. Future studies were encouraged to provide quantitative evidence regarding the interrelationships between nocturnal scratch and other disease domains as part of the clinical validation package.

ITF Pre-Meeting Question 1.1: Characterisation of the connection between itch, scratch and associated impact on patient well-being e.g., as a consequence of sleep disruptions, daytime fatigue and skin trauma is paramount. Please discuss whether the available data as published in the literature and as part of the DiMe study are considered sufficient to support an expectation that 'nocturnal scratch' as an outcome parameter could inform regulatory decision making in terms of efficacy of IMPs to treat AD? Do you consider further studies to characterize the interrelationship?

The ITF requested clarification if the DiMe survey fully looked at interdependencies between itch/scratch and other symptoms of the disease, as the limited number of responses may not be sufficient to use such an enriched endpoint as a co-primary endpoint. The Applicant acknowledged that further studies could provide useful supplementary evidence as it is not clear if survey data are robust enough to explain the relationship between different aspects of the disease.

The ITF agreed that scratch is a valuable component of the disease to be targeted independently to add value to existing endpoints. Whether scratch should be used as a secondary or exploratory endpoint will depend in part on the evidence presented for qualification. ITF noted in the briefing document there was a lack of evidence on sensitivity to change to support use a secondary endpoint; Applicant explained that the consortium effort is based on publicly available data and the DEEP framework but future qualification requests would include additional data such as sensitivity of nocturnal scratch to detect change.

ITF Pre-Meeting Question 1.2: How does the observed lack of consistency between AD disease severity and severity of nocturnal scratch impact on the ability to qualify a nocturnal scratch measure as efficacy outcome in studies aiming at demonstrating efficacy to treat AD?

Applicant clarified that a strong relationship was not observed in *qualitative* interviews; however, in the *quantitative* survey and literature, there was a strong link between disease severity and reported frequency of nocturnal scratch. ITF noted that the difference between qualitative and quantitative findings is not unexpected. ITF confirmed this has been clarified and will evaluate data when the Applicant submits a qualification request in the future.

ITF Pre-Meeting Question 1.3: You mention that "Overall, ~65% of participants reported nocturnal scratching >1 day/week, resulting in ~1 – 1.4 hours of sleep lost per night.". In light of these data, would the envisaged Context of Use of a nocturnal scratch DHT measure aim at generating data to support a broad AD treatment indication or rather for a symptomatic indication when deployed in clinical trials with an enriched target population, i.e., AD patients with a high symptomatic burden of nocturnal scratch?

Applicant clarified that the measure is intended for broad population and ITF confirmed this was clarified with no further questions.

ITF Pre-Meeting Question 1.4: You mention that "About 50% [of patients] reported willingness to use technology to measure nocturnal scratch and ~25% were unsure". These figures seem to illustrate significant challenges for broad application, and a potential for a high drop-out rate; did you explore further reasons for low acceptability, and did you explore options to improve acceptability, e.g. by improving ergonomics of the sensors?

Applicant emphasized the importance of acceptability for patient/caregiver and importance of developing a tool together with patients to ensure broad application. Applicant clarified that DiMe survey data was based on nonspecific questions which ITF agreed are not very helpful to understand the acceptability. Applicant also outlined the most frequent concerns captured (physical discomfort and sleep interference); in 2 studies [redacted] participants confirmed overall comfort of a wrist-worn device and willingness to wear continuously. ITF noted that Patient representative (unable to join today) provided input for similar submissions and during qualification workshop in Apr 2023 about concerns on ergonomics and privacy – good to see data presented by the Applicant and ability to characterize this as part of validation.

ITF Pre-Meeting Question 1.5: Clinical validity of a nocturnal scratch measure will be dependent on the integrity of the accompanying sleep assessment. Please provide further details on the strategy to support validity of sleep assessment and what role an assessment

of consequences of sleep disturbances on the daytime functioning of AD patients could have in the context of the envisaged qualification of nocturnal scratch as an outcome measure in AD studies.

The Applicant emphasized that the total sleep opportunity (window of time in which nocturnal scratch is measured) must be validated for a valid nocturnal scratch measure. Applicants' position on additional sleep assessment measures is that whilst valuable and should be collected if possible in future studies, it is not needed to qualify nocturnal scratch as secondary endpoint. ITF seemed to agree and suggested that further exploratory data would be helpful to understand relevant patterns between different disease domains.

Topic 2: Proposed Terminologies and Ontologies

Applicant Question 2: Does the Agency agree with the proposed terminologies and ontologies defining digitally measured nocturnal scratch used in the context of a measure for drug development?

Applicant's Position

A shared measure ontology is highly desired and arguably necessary to support adoption and use of this measure. Notably, a mutually agreed upon ontology will enable:

1) the generation of comparable data necessary to define the natural history of AD as relevant to these concepts, typical within patient variability, across population variability, and minimally clinically important differences in different context of use, and

2) stakeholders, including regulators and health authorities, to assess nocturnal scratch data consistently across studies.

The applicants propose the use of nocturnal scratch, with the realization that the use of the term will need to be further defined in the context in which it is being used.

ITF Discussion - Key Points on Topic 2

ITF Pre-Meeting Question 2.1: The proposal and discussion on the proposed terminologies and ontologies is acknowledged. As already mentioned in the validation comments, it is not fully understood why the term 'nocturnal' scratch is considered appropriate to describe scratch activity during sleep periods which can occur also during daylight hours. Conceptually, studies to support validity of the 'nocturnal' scratch measure will then also need to include AD patients who need to sleep during daylight hours due to working patterns, in order to characterize that the daytime period during which sleep occurs has no independent impact on sleeping and scratching patterns. Please discuss in terms of appropriateness of terminology as well as scientific considerations for evidence generation for qualification.

ITF acknowledged the Applicant's position and understood the reasoning and information provided; they also could envisage a more appropriate term. However, at this time they could also "live with" nocturnal scratch as the term has been used in the scientific literature for quite a while and describes the majority of the population, with the realization that there would be additional context provided by the sponsor.

Topic 3: Context of Use

Applicant Question 3: Does the Agency agree with the proposed context of use and clinical meaningfulness of the nocturnal scratch and sleep measure/s?

Applicant's Position

The intended use of the novel measures of nocturnal scratch and sleep disturbances are to provide quantitative measurements of these symptoms in clinical trials in response to treatment of a given disease. Specifically, in this instance, the intended use is to quantitatively measure a therapeutic response to treatment in nocturnal scratch in persons with mild to severe AD. Thus, understanding the nocturnal scratch and sleep disturbances as symptoms in patients allow for additional understanding of the disease, allowing for more appropriately targeted treatment times to ultimately improve outcomes.

ITF Discussion - Key Points on Topic 3

ITF Pre-Meeting Question 3.1: The context of use proposal does not specific whether the outcome measure is intended to be qualified as primary or secondary endpoint in AD studies, and also lacks information on the type of study in which the measure will be deployed (e.g. Phase 2, confirmatory, broad mild to severe AD population or enriched population with relevant itch/scratch symptoms). Please discuss current intentions and implications of a refined target Context of Use for the evidentiary requirements for qualification.

The refined context of use proposed by the applicant is: *secondary endpoint to measure efficacy of treatments of AD in pivotal confirmatory clinical trials in mild to severe AD patients 2 years and older.*

The applicant believes that nocturnal scratch has sufficient evidence in the literature to support it as a secondary endpoint, providing key objective and quantitative support to current primary efficacy endpoints and providing additional insights into symptomology of the disease for the patients. It is important to recognize that the context of use may be further refined in the future depending on the specific clinical trials the individual sponsors that are part of may discuss in the future.

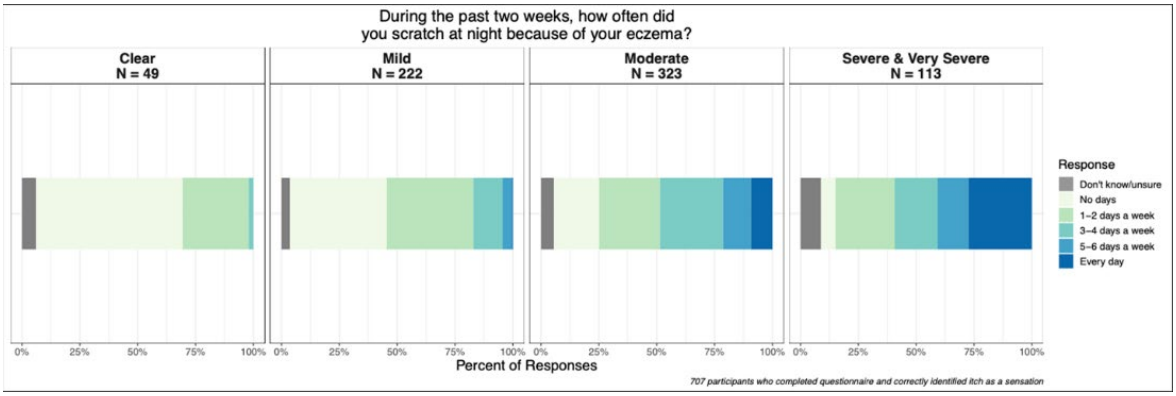
ITF agreed the potential is there and agreed with the proposed context of use subject to additional detail which would be needed for individual use cases, e.g. with a view to demonstrating the ability to detect change and to characterising the MCID.

Regarding the use of nocturnal scratch as a primary endpoint, the applicant agreed it would most likely be used as a co-primary vs. a standalone primary endpoint at this time. The sponsor would be required to provide the appropriate justification for their specific context of use of the endpoint. It is envisaged that additional evidentiary requirements would be needed highlighting the clinical meaningfulness of the measure as well as the benefit associated if used as a primary or co-primary endpoint.

ITF Pre-Meeting Question 3.2: You mention: 'However, while we do realize that this is not the only symptom associated with the disease, it serves as a more complete picture of the disease and the improvements realized with treatments.' Given that only ~65% of participants in the DiMe study reported nocturnal scratching >1 day/week, resulting in ~1-1.4 hours of sleep lost per night, and that scratch/itch intensity was found not to increase in parallel with AD disease severity as characterized by established clinical scores, the notion of a more complete picture appears questionable. Please discuss.

The Applicant reiterated the response to questions 1.2 and 1.3 that showed that scratch frequency increased with AD disease severity. The Applicant further clarified that Survey Question 11 was not originally included in the Cesnakova, L et al publication due to space constraints. However, the data

are available for download (https://datacc.dimesociety.org/digital-measures-nocturnal-scratch/#research) with results summarized in the graph below:



The applicant clarified that the "65% data" represents an all-comers population including the clear and mild AD disease categories. The percentage of patients reported nocturnal scratching in the moderate and severe and very severe AD categories is significantly higher.

ITF Pre-Meeting Question 3.3: Given that a substantial part of the overall AD population appears not to perceive itch/scratch as a key symptom, would the study population need to be limited/enriched to those patients considering itch/scratch as a key impediment to their QoL? It appears that demonstration of correlation between scratch and sleep disturbance and impact on daily life is key for qualification.; Therefore, robust validation of the ability to reliably measure sleep parameters appears to be of similar importance as scratch parameters and the demonstration of impact of scratch and sleep disturbance on QoL of AD patients would be key to support e.g. validity as a primary endpoint in a confirmatory study. Please discuss.

The applicant emphasized that Nocturnal Scratch is a key symptom in AD that not only impacts the disease, but the persons and caregivers QoL.

Per the DiMe survey and within in the literature, as presented within the briefing book, scratch is a key symptom of AD. Moreover, not only does it impact patients' QoL, sleep, fatigue, work, school, it is a key perpetuating aspect of the disease. As highlighted within the briefing book, scratching damages the epidermal skin barrier facilitating a downstream cascade of physiological actions upon the insult. This cascade can include damaging the outer skin layer, leading to allergen and bacterial infiltration (eg *Staphylococcus aureus*), inflammatory and immune responses, downstream signaling (JAK/STAT, MAPK/ERK, etc.), stimulation of itch sensory neurons and subsequent nerve fiber-brain signaling.

The applicant agreed that further studies could/will provide useful supplementary evidence to better characterize the relationship between itch, scratch, disease severity and patient well-being including sleep disruption, daytime fatigue, and skin trauma, especially as it relates to more specific contexts of use that sponsors may propose. However, these studies do not preclude the current need and value of nocturnal scratch in current clinical trials.

Topic 4: Development and Validation of Digital Measures

Applicant Question 4: Does the Agency agree that the evidence visualized in Table 4.1 is, in principle, appropriate for development and validation of digital measures of nocturnal scratch in AD that can be used as secondary endpoint(s) to support labelling claims related to how a patient functions?

Applicant's Position

The proposed pathway to develop and validate the selected digital measures is outlined in Figure 4.1 and Table 4.1 (figure/table numbers as per the briefing document). The following sections provide additional high-level information on this approach.

Table 4.1 (from the briefing document) provides a breakdown of the proposed pathway described in the sections above to validate the chosen nocturnal scratch measures as potential secondary endpoints in clinical studies of AD and to support labelling claims related to how a patient feels and functions.

Study	Activity	Objective	Summary
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.
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
		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
		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: o PROs (e.g. NRS Itch) o Skin lesions • Primary/secondary efficacy assessments, e.g. EASI SCORAD or vIGA-AD
	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. o Literature supporting the meaningful changes observed in standard sleep and scratch/lesion measures

Table 4.1. Summary of proposed analytical and clinical validation studies

ITF Discussion - Key Points on Topic 4

The ITF had no overarching concerns with the strategy proposed in Question 4. The discussion centred on the use of natural history studies and discussions regarding the derivation of the minimally clinically important difference (MCID). ITF acknowledged that AD is not a progressive disease and is one that is often in flux and has "flares". In addition, it was agreed that analytical validation with patient coefficients of variation would cover variability of disease with respect to flares. ITF were open to alternative complementary methods to determine MCID, however, additional detail, context and discussion would need to take place.

ITF Pre-Meeting Question 4.1: The high-level strategy outline of Concept Elicitation- DHT feasibility- Analytical Validation and Clinical Validation appear sound; Fig 4.1 does not mention testing on the ability to detect change in terms of natural history of the disease, i.e. not in response to treatment; please clarify.

The Applicant acknowledged that there is value in natural history studies, however the disease is atypical in that it is cyclic in nature as it resolves over time and then can flare and reappear. Therefore, it may be challenging to evaluate and establish specific change in terms of this type of study. However, the applicant feels that understanding the nature of nocturnal scratch would provide value, potentially even identifying the disease at early onset. Further studies could provide useful supplementary evidence as it is not clear if survey data are robust enough to explain the relationship between different aspects of the disease.

ITF agreed that AD is not a progressive disease, and a natural history study alone, while useful, would not be fully informative, but inquired as to whether nocturnal scratch would assist and help understand the aspects of flares/remission over time. ITF also concurred that additional studies and work over time would be acceptable and valuable to understand this, while not necessarily required to use the measures currently. Moreover, the validation plans for nocturnal scratch should cover the disease regarding flare and remission periods.

ITF Pre-Meeting Question 4.2: Please discuss in more detail possible anchor-based and distribution-based methods which could be applied to characterize MCID.

The applicant shared that while there is value in comparing nocturnal scratch to the traditional anchors of Patient Global Impression of Severity (PGIS)/ Patient Global Impression of Change (PGIC), Patient Reported Outcomes (PROs) and Clinical Outcome Assessments (COAs), these may be challenging in that nocturnal scratch is difficult to capture, and those with AD often scratch without the realization that they are scratching. In addition there is the added complexity to recall nocturnal scratch (persons with AD have commented that they are asleep so it is challenging). Moreover, the changes in scratching may occur earlier than the perception by the person. Therefore, the applicants proposed evaluating PPI and Idio scale as potential methods that would provide value to further assess the MCID.

The ITF asked for additional context around the use, and the applicants conceded at this time this was still in concept and additional evidence would need to be presented to demonstrate the value. ITF expressed that what was designed would need to be relatable to patients and should show understanding if the meaningful changes are the same across the different states of the disease. ITF highlighted that the concepts and methods would need to be well defined and to be aware of artificial inference. ITF noted that as a concept this is valid but there may be challenges as the changes may be small. ITF was open to alternative and/or complementary methods to determine MCID, however additional detail, context and discussion would need to take place.

Topic 5: TSP and the Addition of a New Definition Block

Applicant Question 5: Does the Agency agree that the addition of a new definition block, including a new context of use and disease, Psoriasis, can leverage an established TSP and subsequent instrumentation block for the nocturnal scratch wrist worn accelerometers (new disease; same TSP and Instrumentation blocks)? Are there any key factors the applicant needs to consider in this scenario?

Applicant's Position

Certain Meaningful Aspects of Health and Concepts of Interest may be relevant to patients with different diseases. Therefore, the same instrumentation block and target solution profile may be used

to collect the measure in those new disease areas. Once a certain technology and validation standards have been validated to collect a specific measure, it should be able to do so in conditions/disease that differ from the initial one, unless there are significant differences between the population characteristics (e.g., adult vs paediatric patients) or disease characteristics relevant to the concept of interest. The concept of leveraging prior information and validation data sets that sit at the heart of the Stack model becomes key in these cases to enable re-use of TSPs and instruments with a fit for purpose validation framework. The Applicant would like to re-use established TSPs and instrumentation blocks (especially those which already have received health authority qualification or feedback).

ITF Discussion - Key Points on Topic 5

ITF Pre-Meeting Question 5.1: Scratch movements and movements defining the detection of 'being awake' could differ between conditions and therefore reliable detection by the DHT (device + algorithm) may not be a given. Table 5.1 proposed that no feasibility testing or analytical validation e.g. by limited comparability studies would be required due to the similarity between AD and Psoriasis. Please discuss whether such justification (e.g. by literature evidence?) is available for this conceptional case, or whether limited 'comparability studies' may be needed in this case and may be advisable generally when considering addition of a new definition block.

As an example of how to use the stack model and re-use evidence, the applicant provided additional discussion regarding psoriasis, including the similarities and minor differences regarding the conditions. The ITF acknowledged that they felt there was value in the stack model and that it was indeed helpful to be able to "re-use" data. However, ITF noted that there may need to be bridging data/comparability studies for new conditions; in this instance it was noted that there are different locations and scratching patterns that may be observed in psoriasis. Moreover within-patient coefficient of variation would be of value to capture. So, while in concept this is valuable, bridging studies would provide reassurance of the validation and will likely be needed.

Topic 6: TSP and the Addition of New Instrumentation Blocks

Applicant Question 6: Applicant Question: Does the Agency agree with the addition of a new instrumentation blocks to an existing TSP (…) without the need of an update to the qualification procedure as long as the new instrumentation block complies with the requirements in the TSP(…) (and other relevant guidance)? Are there any key factors the applicant needs to consider in this scenario?

Applicant's Position

The TSP determines the key performance characteristics that are reviewed and agreed to by the Agency reviewers in a qualification procedure. These performance characteristics or requirements are part of the TSP in the stack model. The evidence in the instrumentation block demonstrates how a specific instrument complies with the key performance characteristics set in the TSP and provides the evidence to demonstrate the TSP is met. In addition to the performance characteristics, the instrumentation solution needs to also undergo computer system validation and comply with ICH E6 requirements of good clinical practice.

The Applicant would like to leverage established TSPs (especially those which already have received health authority qualification or feedback) while changing components of the instrumentation block and the additional evidence that would be needed to be presented to inspectors and marketing authorization application (MAA) clinical reviewers to support the use of a new instrumentation block while retaining the same TSP and measurement definition block are proposed below. Regarding the 'minimal comparability studies needed'; it would be expected that the applicant demonstrate

equivalency regarding the specific sensors and measures from the DHT to that of one of the established DHTs within the instrument blocks previously used, as well as captured by the prespecified TSP parameters. In the future this will be captured by a qualification protocol when that is developed.

Study	Activity	Objective	Summary	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.	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	Supplemental Evidence Required†	No Additional 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	Supplemental Evidence Required†	No Additional Evidence Required*
	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	No Additional 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	No Additional Evidence Required*	Supplemental Evidence Required†
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)	No Additional Evidence Required*	Supplemental Evidence Required†
	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, i.e. o PROs o Skin lesions	No Additional Evidence Required*	No Additional Evidence Required*
	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	No Additional Evidence Required*	No Additional Evidence Required*

Table. Summary of proposed analytical and clinical validation studies: evidence that can be re-used in cases of use of a new or updated instrument while keeping the same TSP and measurement definition block. *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.

ITF Discussion - Key Points on Topic 6

ITF Pre-meeting Question 6.1: Overall, the position statement provides a clear basis for discussion. For changes in hardware/device, no additional evidence requirements for analytical validation are foreseen 'if the new instrument meets the previously qualified TSP and demonstrates equivalence to previously used instrument'. Please clarify how demonstration of equivalence to previously used instrument is envisaged.

The Applicant provided clarification on how demonstration of equivalence between new DHTs and/or changes in previously used DHTs is envisaged. In particular, the Applicant explained that the framework for evaluating changes to DHTs consists of evaluating whether the changes between DHTs affect the performance specifications previously established in the TSP. This evaluation is envisioned to consists of three types of testing: non-clinical benchtop testing, clinical bridging studies, or re-validation with the type of testing being dependent on the nature of the change. Additionally, the Applicant highlighted that the focus of the paradigm would be on technical comparisons between DHTs/DHT versions and a previously validated DHT instead of re-use of a "ground truth". The Applicant also walked through the example of a change in battery components and how such a change might be evaluated via benchtop testing to verify battery life to demonstrate that the change is not anticipated to affect the fitness of the DHT for use in measuring the aspect of health.

ITF expressed positivity in the large potential for the described paradigm. ITF agreed that if a link between observed variability in analytical validation studies and technical performance characteristics was observed, then bench testing may be sufficient. However, ITF also noted that for more significant changes such as using a different DHT type to measure the same aspect of health, this may require additional validation. ITF noted that it is desirable for Applicant to aim to develop DHT agnostic measurement solutions and the stack model is anticipated to support this. ITF was very much interested in the stack model and re-use of evidence, but also needs evidence to provide reassurance that the concept leads to good regulatory decision-making.

ITF also raised concern that comparisons back to previously validated DHT may lead to the propagation of error between generations of DHTs. However, the ITF also acknowledged that although the addition of errors needs to be considered, theoretical errors may be high but in practice, may not be relevant. ITF encouraged the Applicant to consider defining performance characteristics that can guarantee the measurement performance.

Final Comments

The overall tone of the meeting was positive and collaborative.

EMA/ITF members and the Applicants appreciated engaging in the DEEP pilot and having the opportunity to explore the DEEP platform prototype.

It was agreed to arrange a meeting on the DEEP platform separately from these scientific discussions.