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4 Draft qualification opinion

5 Paediatric Ulcerative Colitis Activity Index (PUCAI)

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Keywords	Paediatric ulcerative colitis activity index, qualification opinion , clinical outcome assessment

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[1] Last day of relevant Committee meeting.
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Introduction

This is a non-invasive clinical disease activity multi-item index aimed to reflect the severity of ulcerative colitis (UC) in children. It is aimed to be discriminative (i.e. evaluating disease activity for judging study entry) and evaluative (as an outcome measure in paediatric UC with and without endoscopic assessment)

Summary

The PUCAI measures disease activity in pediatric UC (Turner D et al. Gastroenterology 2007). It was developed to act as an accurate non-invasive (i.e. suited for children) reflection of endoscopic inflammatory activity and has proven to have high reliability and responsiveness to change in clinical trials. After its publication, it has also proved to be highly accurate in predicting clinical course of pediatric UC and hence was incorporated in international clinical algorithms for the management of acute severe ulcerative colitis and ambulatory pediatric UC.

The PUCAI is proposed to be used as an endpoint in clinical research of pediatric UC combined with endoscopic evaluation or independently as a stand alone scoring system when endoscopy is not warranted. It is also proposed to be used as a discriminative measure at baseline for determining disease activity as part of eligibility criteria of clinical trials and for evaluative purposes in reflecting change over time. It has been successfully used thus far in multiple clinical studies, accurately reflecting endoscopic disease activity.

Questions from the applicant

Purpose:

1. Using the PUCAI as the primary outcome measure in clinical trials of pediatric UC, as a proxy for endoscopic assessment when colonoscopy is waived (e.g. studies that test therapies already shown to induce mucosal healing in adults and if they do not represent a new drug category) or, as a secondary measure, in those study visits that do not include endoscopic assessment.
2. Using the PUCAI to classify children into disease activity states (remission, mild, moderate and severe) to screen eligible children for enrolment.

COI: DT and AMG are inventors of the PUCAI which is copyrighted to the hospital for sick children, Toronto.

Summary of supporting text: It is widely accepted in adults that the primary outcome of UC clinical trials should be based on evaluating the colonic mucosa. Children, however, carry unique considerations, which reduce feasibility of trials and pose significant ethical challenges. The eligible population for recruitment is small given the lower number of incident and prevalent pediatric IBD cases compared with adult cases. Parents, concerned about potential side effects of therapies and the additional invasive tests, are more reluctant to have their children engaged in intervention trials than are adult patients. Many clinicians also express similar hesitancies in the face of invasive procedures in children that require general anaesthesia. The fact that pediatric trials are often only confirmatory to similar larger adult trials should be used as an advantage to balance the challenging recruitment in children. These considerations are fundamental when determining primary outcome measures in order to increase feasibility of paediatric trials and thus avoiding the current situation that many medications are given to children “off-label”.

Clinical disease activity indices are valuable tools to evaluate disease activity in UC. Unlike Crohn's disease, UC has a more homogenous presentation and the vast majority of patients in complete sustained clinical remission have a normal, or near normal, endoscopic appearance. There are now multiple different studies evaluating the performance of the PUCAI in the different scenarios, showing high clinimetric properties and excellent correlation with the presence of colonic inflammation on endoscopic evaluation (1-17) (figure 1). The PUCAI performed well also when completed directly by the patients (9), and has been shown to correlate with patient-reported quality of life scales (10).

Validity (construct, discriminative and predictive): The PUCAI is tightly correlated with endoscopic appearance of the colonic mucosa (1, 17) and the correlation with the mayo score is as high as 0.95 (1, 12, 17). Predictive validity of the PUCAI is high and may be even higher than endoscopic score as found in multiple studies. The T-72 infliximab trial in children with UC showed that PUCAI-defined remission was not inferior to sigmoidoscopy in predicting 1-year steroid-free sustained remission (12), a finding recently replicated also in ambulatory UC children (14). The PUCAI strongly predicted the need for short term treatment escalation in pediatric UC (18) and the type of surgical intervention, when needed (11). In two independent cohorts of children requiring admission for intravenous treatment of corticosteroids for UC exacerbations, the PUCAI has shown strong predictive validity of outcomes important to patients, accurately identifying children who will require treatment escalation to second line medical therapy or colectomy, both by discharge and up to one year post discharge (2, 7). In this setup, the PUCAI has shown to have superior predictive validity to five fecal biomarkers, including calprotectin (15, 17).

The corresponding PUCAI cut-off scores of remission (<10 points), mild (10-34 points), moderate (35-64 points) and severe (≥65) disease have been validated in several cohorts and found to have sensitivity, specificity and area under the ROC curve of >95% (1, 5, 17). In the regulatory T72 trial evaluating the effectiveness of infliximab in pediatric UC, the PUCAI determined week 8 remission rate was 33%, identical to the rate of complete mucosal healing found by sigmoidoscopy (19) (figure 1). Similarly, the week 12 remission rate in a clinical trial evaluating Beclomethasone 17,21-dipropionate (BDP) in children with UC, was similar whether determined by sigmoidoscopy or the PUCAI (20), as well as when comparing sigmoidoscopy, ultrasound and the PUCAI (21).

Reliability: Inter-observer reliability of the PUCAI has shown to be high in the development and the evaluation cohorts of 215 children with UC (intraclass correlation coefficient=0.95) (1). The test-retest reliability was evaluated in three different cohorts showing similar performance of ICC between 0.89-0.94 (1, 5, 17).

Responsiveness: Responsiveness was shown to be very high at repeated visits of 74 children using several statistical methods and the correlational, distributional and anchor-based approaches (1). Similar psychometric properties were shown in another cohort of registry cohort (5). The PUCAI captures day-by-day change in disease activity in acute severe colitis children (2, 7) and thus incorporated in treatment strategies in this cut-off (22). The minimal clinically important difference has been successfully defined as a change of at least 20 points (area under the ROC curve of 0.97) (1, 4-6, 17).

CHMP answer

The PUCAI (pediatric ulcarative colitis activity index) is a well-established outcome measure in pediatric UC, and has been included in the current UC guideline as a recommendation ("in children a validated paediatric colitis activity index has been evaluated and approved omitting the necessity for endoscopic follow up").

The proposal of the applicant includes, that the PUCAI should be used as primary outcome measure in studies in paediatric UC, if the effects on mucosal healing have already been established, and hence to establish the PUCAI as primary outcome measure in paediatric clinical trials as a proxy for endoscopic assessment when colonoscopy is waived, and – with regard to the thresholds for activity states (remission, mild, moderate and severe) – as a screening tool for eligibility into clinical trials. The proposed "context of use" (or the current "purpose statement" as submitted) also includes the assumption that in a certain context extrapolation from adults to children could take place (and therefore endoscopy evaluations would not be needed), and hence the PUCAI be used as "surrogate" for the overall evidence of clinical outcome.

It is also proposed that the PUCAI is used as secondary endpoint "in those study visits that do not include endoscopic assessment"

This latter statement refers to the use of the scale in a situation/clinical trials in which endoscopy is included as primary outcome measure. Why the use should be restricted to the visits that do not include endoscopic assessment is not understood. However, any statement on the use as secondary endpoint appears to be unnecessary in a situation when the instrument chosen is qualified to be used as primary endpoint.

The PUCAI is a 6-dimensional tool, rating the severity of the following symptoms/disease characteristics of UC: abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal stools, and assessment of limitations of activity of the patient. The sum of the score ranges from 0-85; however, there are not 85 severity grades, due to the rating restrictions (e.g. pain is rated 0 if there is no pain, 5 if pain can be ignored, and 10 if it cannot be ignored).

For the qualification of the PUCAI as outcome measure and as activity classification tool, the applicant is referring to the existing validation work, composed entirely of literature references.

The applicant is able to refer to results showing a high correlation of the score to other scores used in the indication (e.g. the Mayo score, clinical indices), endoscopy outcomes ("mucosal healing"), need for treatment escalation, and long-term outcomes such as need for surgery. Superiority to faecal biomarkers in this respect has also been documented. This has been shown across the severity grades and with different types of medication, although the mainstay of the data is derived from the T-72 study which evaluated efficacy of infliximab in children

The established cut-off scores for the PUCAI defined severity stages (<10 points=remission; 10-34 mild disease; 35-64 moderate disease; ≥65 severe disease) are based on three references only (according to the applicant; however, 1 study was conducted in adults!), showing sensitivity, specificity and area under the ROC curve of >95%. The definition of remission is also supported by the high correlations of remission in the T 72 trial, and a trial with beclometasone, when compared with sigmoidoscopy. The thresholds are based on the data of about 430 children.

Furthermore, reliability has also been shown to be high (intraclass correlation coefficient 0.95), and responsiveness has generally been determined to be high, with the MID defined as 20 points.

Scientific questions discussed during the qualification procedure:

The applicant was requested to clarify whether the introductory statements called "purpose statements" should indeed be understood as the statements of the "context of use"

As a reply, the applicant brought forward the simpler question whether the CHMP will approve (qualify) this index as a multi-item measure of UC activity, for use in clinical trials. The "purpose statements" below represent the specific roles we intend for the PUCAI in future clinical trials.

- The PUCAI is a very good proxy of mucosal healing and as such should be used as an outcome measure in pediatric trials exempt from endoscopic evaluation, and in visits without sigmoidoscopy
- The PUCAI can be also used to screen patients as having mild/moderate/severe disease state at baseline.

CHMP answer

The proposed context of use has been simplified. The most obvious difference to the statements brought forward initially, is the fact that the reasons for the waiver of endoscopic evaluations in the trials are not included. This is fully agreed with, and was regarded as a potential obstacle for the approval of the statements. Approving reasons for why colonoscopy and endoscopic evaluation shall not be included in pediatric clinical UC trials was regarded to be out of the scope of this qualification procedure, in as it was considered that problems of (partial) extrapolation of efficacy and safety from adults to children, as well as the general need for endoscopic assessment in pediatric UC trials were touched upon. The simple statement that the PUCAI can be used as outcome measure, is a good proxy for mucosal healing and should be used if endoscopic evaluation is not included in the overall evaluation of patients is supported.

Again, the statement is referring to "visits without endoscopy" also, obviously in a situation when endoscopy is used as primary endpoint. As this is also independent of the fact whether endoscopy will in the end be regarded to be the most accurate outcome in paediatric UC trials, the statement can as such be accepted. It is indeed referring to a situation where a more frequent evaluation of the state of a patient is needed than endoscopic evaluation are regarded to be able to deliver, because the frequent conduct of endoscopy in children is burdened with ethical concerns.

SAWP question to the applicant

The intention of the advice should be described more clearly. Does the applicant see a need for qualification in a situation where the index is already included in the existing guideline?

Applicant's reply

In their reply, the applicant stated that they were asking for a comment, based on the published psychometric properties, whether the existing PUCAI is scientifically suitable for use in the context described in the initial application. The PUCAI, which is a physician-based index, is proposed to be used as an endpoint in clinical research of pediatric UC when endoscopy is not warranted such as in certain visits without endoscopic evaluation or in trials of drugs which do not represent a new category and previously evaluated in adults, as articulated in the ECCO statement (Ruemmele et al, GUT 2014). It is also proposed to be used as a discriminative measure for determining disease activity as part of eligibility criteria of clinical trials and for evaluative purposes in reflecting change over time. In trials/visits in which endoscopic evaluation is warranted, it is envisioned that a newly derived PRO (i.e. the TUMMY index) is used in conjunction.

The applicant assumed that a scientific qualification of the psychometric properties of the PUCAI, could assist in the revisions of the EMA guidance on pediatric IBD clinical trial design so the choices are made on solid evidence.

CHMP answer

The applicant has further clarified the proposed context of use. However, contrary to the above general answer (answer to question 1) given, again a context is included which defines a broader context and conditions that had already been abandoned in the above statement. It is, however, considered that the reasons why a clinical trial does not include endoscopic evaluations should not be part of the definition of the context of use. Based on two reasons:

- The scientific evidence provided does not include any conditions for use of the PUCAI and whether it is used as a substitute of endoscopic evaluation or as a supplement.
- The inclusion of statements that in certain situations an endoscopic evaluation is not needed (e.g. when "sufficient" data are available in adults) is not considered appropriate. This qualification procedure is not expected to decide whether in general or in certain situations, extrapolation from adults to children can be regarded to be appropriate (e.g. drug categories which are not considered new). The scope of any CoU statement must therefore be different from the statements given in the ECCO statements, where the main purpose was to define the "most important primary outcome measure" for randomised clinical trials in children with IBD (Ruemmele et al; Gut 2014)

Generally, however, a qualification procedure can be initiated independently from any mentioning of biomarkers and/or outcome measures in any of the EMA guidelines.

SAWP question to the applicant

For the qualification of the severity thresholds: Have the data been derived from patients after treatment only (selection of patients usually occurs before treatment)? Might this have an impact on accuracy?

Applicant's reply

Three different cohorts (2 pediatric and 1 adult) have been used to select and validate the cut-off scores corresponding to remission, mild, moderate and severe (totalling 430 children and 86 adults). The applicant regards it as encouraging that the cut-off values obtained from three different cohorts and scenarios were identical and with high sensitivity, specificity and areas under the curve to differentiate the different categories (>90%). The cohorts included patients representing a typical pediatric cohort of UC. All active patients (used to define the mild, moderate and severe cut-off values) were per-definition before treatment, since active children are never left untreated. Therefore, the main body of data to support the choice of the cut-off values came from children before treatment.

CHMP answer

The fact that the cut-off validation data come from a (mainly) untreated patient population is regarded to be re-assuring. In fact, for the two trials that have these data available, very high AUC-ROC (>0.92; mostly >0.95) values have been determined for all three severity categories (See Turner et al, Gastroenterology 2007; Turner D et al: Clin Gastroenterol Hepatol 2009).

SAWP question to the applicant

Is there a need for support (based on valid data) of the underlying assumption that extrapolation from adults to children is possible if sufficient data on mucosal healing is available in adults? Considering the intention to "extrapolate" the biological mechanism on the mucosal appearance from adults to children: Is there a need for the availability/generation of validation data of the PUCAI in adults before final conclusions on its surrogacy can be drawn?

Applicant's reply

The applicant expressed their view that there are two different concepts here. The first is whether extrapolation from adults the biologic effect of a given drug on the mucosa and the rate of mucosal healing is possible. This has been widely discussed in the ECCO 2014 statement and not in this application (It has been agreed that, at times, mucosal healing can be extrapolated). In this application the applicant claims that in those instances that the agency waives the obligation for endoscopic evaluation, then the PUCAI closely reflects the degree of mucosal healing (Mayo subscore 0 or 1) to an accuracy of ~90%. This is irrespective of the performance of the PUCAI in adults.

Nonetheless, the PUCAI has shown high psychometric properties also in 86 adults undergoing colonoscopy, as compared with all other existing adult UC indices (CGH 2009;7:1081–1088) and in 153 adult UC patients with acute severe colitis (Koslowsky et al. The Use of the PUCAI in adults with acute severe UC; DDW, May 4th 2014, Chicago, USA; Abstr Su1112).

CHMP answer

The applicant has correctly stated that extrapolation as such is not within the scope of this qualification procedure. However, the applicant also states that in instances where there is a regulatory waiver of endoscopic evaluations in clinical studies, the PUCAI can serve as a proxy for endoscopic evaluation. However, this introduces even a new condition into the potential context of use, which is also considered to be outside the scope of this procedure and also without the scope of any of the evidences presented. As already mentioned above, the reason why endoscopy is waived should not be part of any statements of the context of use of the PUCAI, but should refer to the fact that endoscopic evaluation is not included for whatever reason.

With regard to adults, it is agreed with the applicant, that the PUCAI also possesses potential for its use based on the limited data available.

Additional material presented by the applicant during the discussion meeting

The applicant has presented the material in support of the qualification of the PUCAI in a more systematic manner during the oral hearing. Scientific literature not previously included in the argumentation was, however, not presented.

Several open questions could be answered and clarifications be provided.

CHMP Opinion

Contrary to a situation when a new outcome measure/clinical activity index is developed with the purpose of gaining regulatory qualification approval, the validation of the PUCAI has been based on the

presentation of literature only. However, the applicant has shown that, since the initial development of the score in 2007 (according to the publication date), a wealth of validation data have become available that is unanimously supporting its validity.

The applicant has shown that the item generation, item reduction, and final weighting of the items included into the score have been done according to state of the art methods.

Cut-off values have been accurately designed and finally been validated in accurate manner.

Reliability and responsiveness have been tested accurately with acceptable results.

In fact, responsiveness has been shown to be higher than with other clinical indices (albeit this was shown in adults).

The overall discriminate validity (differentiating remission from active disease) has been shown to be highest compared to all other commonly used clinical disease activity indices.

A high correlation of the PUCAI with colonoscopic outcomes in children was demonstrated in clinical trials with a variety of different therapeutics.

The predictive value of the index is higher than any of the commonly used faecal markers of disease activity, such as e.g. CRP and calprotectin. It also predicts the need for treatment escalation.

The PUCAI has shown to have a high predictive correlation to long-term outcomes, such as 1-year sustained steroid free remission, or 1-year need for salvage therapy.

Potential missing items in the validation appear to relate to a clear differentiation between age ranges. It remains therefore not fully clear whether validity is the same in the age group of very young children, which mostly present with rather high severity and vast extent of the disease.

Overall, the following statements of context of use can be supported:

1. The paediatric ulcerative colitis activity index (PUCAI) can be used as the primary outcome measure in clinical trials of paediatric UC as a proxy for endoscopic assessment when colonoscopy is waived with appropriate justification

2. The PUCAI is suitable to be used as reliable efficacy evaluation in visits during which endoscopy is not performed in clinical trials of paediatric UC where endoscopy is used as primary outcome,

3. The PUCAI can be used to screen paediatric UC patients in order to grade disease activity into mild, moderate or severe.

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