PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A prospective, observational, longitudinal study in paediatric patients with moderate-to-severe atopic dermatitis (PEDISTAD): study objectives, design and methodology: a study protocol
AUTHORS	Paller, Amy; Guttman-Yassky, Emma; Irvine, Alan; Baselga, Eulalia; de Bruin-Weller, Marjolein; Jayawardena, Shyamalie; Zhang, Annie; Mina-Osorio, Paola; Rizova, Elena; Ozturk, Zafer

VERSION 1 – REVIEW

REVIEWER	Steven Feldman Wake Forest School of Medicine Winston-Salem, NC 27104, USA I have had speaking, grant and consulting support from Sanofi & Regeneron. I have received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Alvotech, Leo Pharma, BMS, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Ortho Dermatology, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. I also consult for others through Guidepoint Global, Gerson Lehrman and other consulting organizations. I am founder and majority owner of www.DrScore.com. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment.
REVIEW RETURNED	16-Aug-2019

GENERAL COMMENTS	This study protocol says that the study will result in a better understanding of long term moderate to severe atopic dermatitis outcomes, but the study also says that no specific hypotheses will be tested. I'm left wondering what we will really know if no specific hypothesis is being tested.

REVIEWER	Mark Jean Aan Koh KK Women's & Children's Hospital
REVIEW RETURNED	31-Aug-2019

GENERAL COMMENTS	A very comprehensive, well-planned study involving a large cohort from multiple countries and multiple centers addressing the long-term outcome of moderate-to-severe AD in infants and children. So far, this data is lacking in large cohorts. Some further comments include:

	1. Inclusion criteria of moderate-to-severe AD according to investigator's assessment. There should be a more objective inclusion criteria e.g. using SCORAD, EASI, BSA 2. Exclusion criteria of concurrent participation in interventional trial - if the child also enters into an interventional trial during the 5 years study period, is the child removed from this study? 3. Elaboration of the biomarker sub-study may be useful including the biomarkers to be studied 4. Does systemic treatment include new biologics, or only phototherapy and systemic immunomodulators. A list of systemic immunomodulators should be also provided.

REVIEWER	Cataldo PATRUNO Department of Health Sciences, University Magna Graecia of Catanzaro, ItalyCataldo Patruno worked as an expert and as a speaker for Sanofi
REVIEW RETURNED	27-Sep-2019

GENERAL COMMENTS	This is an excellent project. However, it would be necessary to be clearer about the inclusion criteria, in order to make patient selection uniform. For example, regarding the evaluation of gravity. What is meant by moderate-severe atopic dermatitis? Is it better to use SCORAD or EASI? What is the critical value?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Steven Feldman

Institution and Country:

Wake Forest School of Medicine

Winston-Salem, NC 27104, USA

Please state any competing interests or state ‘None declared’: I have had speaking, grant and consulting support from Sanofi & Regeneron. I have received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Alvotech, Leo Pharma, BMS, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Ortho Dermatology, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. I also consult for others through Guidepoint Global, Gerson Lehrman and other consulting organizations. I am founder and majority owner of www.DrScore.com. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients’ adherence to treatment.

This study protocol says that the study will result in a better understanding of long term moderate to severe atopic dermatitis outcomes, but the study also says that no specific hypotheses will be tested. I'm left wondering what we will really know if no specific hypothesis is being tested.

Response: We thank Dr. Feldman for his comment. This observational study was not designed to test an a priori hypothesis, but to collect real word data that would be reported as appropriate, e.g., in terms of summary statistics. Although no specific hypotheses will be tested, the study has specific objectives that aim to address the substantial need for a better understanding of AD characteristics and progression, including patient and caregiver burden, in pediatric patients with moderate-to-severe AD who initiate, or are candidates for, systemic therapy. Specifically, the primary objectives of the study are to describe the characteristics of pediatric patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical therapies or when those therapies are not medically advisable, and to evaluate the time course of AD and selected atopic comorbidities. Secondary objectives include to characterize disease burden and unmet need, to describe real-world treatment patterns, and to document the real-world effectiveness and safety of treatments. By collecting information about clinical characteristics, including patient- and care-giver reported outcomes, physician-assessed clinical severity, safety of currently used medicines and photographs of a representative area affected by AD (at select centers), over time, the PEDISTAD study aims to address the lack of robust and longitudinal long-term data related to AD characteristics, disease progression, development of comorbidities and the typical clinical practice with currently available treatments in children with AD. *To better highlight what this study will add, a table listing the primary and secondary objectives of the study has been added to the manuscript.*

Reviewer: 2

Reviewer Name: Mark Jean Aan Koh

Institution and Country: KK Women's & Children's Hospital

Please state any competing interests or state ‘None declared’: None declared

A very comprehensive, well-planned study involving a large cohort from multiple countries and multiple centers addressing the long-term outcome of moderate-to-severe AD in infants and children. So far, this data is lacking in large cohorts.

Some further comments include:

1. Inclusion criteria of moderate-to-severe AD according to investigator's assessment. There should be a more objective inclusion criteria e.g. using SCORAD, EASI, BSA

Response: The authors thank the reviewer for his comment and appreciate the suggestion to specify more objective inclusion criteria. The PEDISTAD is a real-world study and, therefore, strict entry criteria are not set. Enrolling physicians are enabled to use their best judgement as to whether a patient meets the inclusion criteria of moderate-to-severe AD using the assessment(s) of their choice. Physician assessment of disease severity will be collected by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline. These assessments can also later be used to assess disease severity in patients over time. Other objective measures of severity may be unfamiliar to clinicians who do not regularly participate in clinical trials in atopic dermatitis, and a lack of familiarity may potentially diminish the reliability of their results. *This rationale has been added to the Discussion.*

2. Exclusion criteria of concurrent participation in interventional trial - if the child also enters into an interventional trial during the 5 years study period, is the child removed from this study?

Response: One of the key objectives of the PEDISTAD is to describe real-world treatment patterns, including therapy dose regimen and treatment duration for pediatric patients with moderate-to-severe AD patients. If a child is concurrently participating in an interventional trial, the number of clinical care visits will be based on the interventional study protocol, which will violate the PEDISTAD study protocol, and physician, patient, and caregiver assessments could be confounded. Therefore, if the child enters into an interventional trial during the 5-year study period, it will be considered protocol violation, and the data will be used only up to the time point that the child enters into the interventional trial.

3. Elaboration of the biomarker sub-study may be useful including the biomarkers to be studied

Response: Pediatric AD presents clinically with a high degree of heterogeneity. Emerging data demonstrate a correlation between clinical and molecular phenotypes (i.e., endotypes). The endophenotype is composed of a collection of biomarkers associated with the clinical phenotype and genotype. In addition to the clinical phenotype, biomarkers and endophenotypes are now considered fundamental to stratify complex diseases into subgroups for which more tailored prevention and therapeutic strategies can be developed.

There is tremendous interest in the identification of biomarkers that could predict the risk of development of comorbidities as well as disease persistence. Due to the waxing and waning nature of this disease and the fact that it can present throughout a lifetime with long periods of remission in some individuals, the ability to predict disease exacerbations or the appearance of associated atopic conditions could have a great impact in the ability to manage the disease for long-term control.

For this reason, we have developed the biomarker sub-study in parallel with the PEDISTAD study to collect blood samples with the objectives of exploring associations between biomarkers of AD and disease state and time course of AD; disease state and evolution of selected atopic comorbid conditions; and effectiveness of specific AD treatments.

A summary of the rationale for the biomarker sub-study and the objectives have been elaborated upon in the Discussion as requested by the reviewer.

4. Does systemic treatment include new biologics, or only phototherapy and systemic immunomodulators. A list of systemic immunomodulators should be also provided.

Response: Systemic AD treatments for this pediatric population (< 12 years) include biologics (currently used off-label), UV therapy, and immunomodulators such as cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, and corticosteroids. The inclusion criteria reported in the Methods section and Table 1 have been updated to include this list to clarify what systemic treatment includes.

Reviewer: 3

Reviewer Name: Cataldo PATRUNO

Institution and Country: Department of Health Sciences, University Magna Graecia of Catanzaro, Italy

Please state any competing interests or state 'None declared': Cataldo Patruno worked as an expert and as a speaker for Sanofi

This is an excellent project. However, it would be necessary to be clearer about the inclusion criteria, in order to make patient selection uniform. For example, regarding the evaluation of gravity. What is meant by moderate-severe atopic dermatitis? Is it better to use SCORAD or EASI? What is the critical value?

Response: The authors thank the reviewer for the comments and appreciate the suggestion to specify more objective inclusion criteria. As noted in the response to Reviewer 2 above, the PEDISTAD is a real-world study and, therefore, strict entry criteria are not set. Enrolling physicians are enabled to use their best judgement as to whether a patient meets the inclusion criteria of moderate-to-severe AD using the assessment(s) of their choice. Physician assessment of disease severity will be collected by Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) percentage affected by atopic dermatitis, which the study investigators can use to assess disease severity at baseline. These assessments can also later be used to assess disease severity in patients over time. Other objective measures of severity may be unfamiliar to clinicians who do not regularly participate in clinical trials in atopic dermatitis, and a lack of familiarity may potentially diminish the reliability of their results. *This rationale has been added to the Discussion.*

VERSION 2 – REVIEW

REVIEWER	Steven Feldman Wake Forest Baptist Health I have had speaking, grant and consulting support from Sanofi & Regeneron. I have received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Alvotech, Leo Pharma,

	BMS, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Ortho Dermatology, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. I also consult for others through Guidepoint Global, Gerson Lehrman and other consulting organizations. I am founder and majority owner of www.DrScore.com. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment.
REVIEW RETURNED	05-Nov-2019

GENERAL COMMENTS	The reviewers' comments were addressed well.

REVIEWER	Mark Jean-Aan Koh KK Women's & Children's Hospital Singapore
REVIEW RETURNED	25-Nov-2019

GENERAL COMMENTS	A very comprehensive and extensive study looking at the trajectory of moderate and severe atopic dermatitis. To improve the study, may want to look at extending the recruitment to other areas of Asia and even Africa, in order to obtain a more global view of this trajectory.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Steven Feldman

Institution and Country: Wake Forest Baptist Health

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Psoriasis Foundation. I also consult for others through Guidepoint Global, Gerson Lehrman and other consulting organizations. I am founder and majority owner of www.DrScore.com. I am a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment.

Please leave your comments for the authors below

The reviewers' comments were addressed well.

Response: No response required.

Reviewer: 2

Reviewer Name: Mark Jean-Aan Koh

Institution and Country: KK Women's & Children's Hospital, Singapore

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

A very comprehensive and extensive study looking at the trajectory of moderate and severe atopic dermatitis. To improve the study, may want to look at extending the recruitment to other areas of Asia and even Africa, in order to obtain a more global view of this trajectory.

Response: The authors thank the reviewer for the suggestion to extend study recruitment to other areas of the world. Currently we are working on feasibility assessments for Korea and China in hopes of including these countries in the PEDISTAD in the future.