



LOI DECISION LETTER

DDTBMQ000078

September 5, 2018

Leslie B. Gordon, MD, PhD
Medical Director
The Progeria Research Foundation
PO Box 3453
Peabody, MA 01961-3453

Dear Dr. Gordon:

We are issuing this Letter of Intent (LOI) Decision Letter to the Progeria Research Foundation, to notify you of our decision on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your LOI submission of June 8, 2018 and have decided to **Accept** it into the CDER BQP¹. We support and encourage your ongoing study of this promising pharmacodynamic biomarker to assess progerin levels in patients who are affected with Hutchinson-Gilford Progeria Syndrome (HGPS) and enrolled in clinical drug development trials.

You have proposed qualification of progerin as a tool to determine that a decrease in progerin levels is an assessment of efficacy of drug intervention in future clinical trials of HGPS. As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable.

Based on our review of the LOI, we agree there is an unmet need and agree with the development of progerin as a pharmacodynamic biomarker that can be used in future HGPS clinical trials.

For the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the scientific issues and the recommendations outlined below. A QP contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned,

¹ In December 2016, the 21st Century Cures Act added section 507 to the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

please include detailed study protocol and the statistical analysis plan for each study as part of your QP submission.

In addition to the qualification effort, we encourage further study of your biomarker including collection of specified exploratory information from the proposed clinical trials. When evaluating biomarkers prospectively in clinical trials, sponsors are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization. If sponsors intend to include analyses of these biomarkers to support regulatory decision making for a specific Investigational New Drug (IND) development program, they should prospectively discuss the approach with the appropriate CDER division. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Leslie Gordon (leslie_gordon@brown.edu), the point of contact for this project, or view the Progeria Research Foundation website at www.progeriaresearch.org.

Biomarker Considerations

Requestor's Biomarker Description: *Progerin is an abnormal splice variant of the inner nuclear membrane protein lamin A. Compared with lamin A protein, progerin is shortened by 50 amino acids near the carboxyl terminus. This affects basic structure as well as post-translational processing of the pre-progerin protein. Progerin is permanently farnesylated, and is therefore associated with the inner nuclear membrane long-term.*

FDA's suggestions for continued development of the biomarker description:

1. We agree with a shortened description of the above biomarker: Progerin is an abnormal splice variant of the inner nuclear membrane protein lamin A.
2. Based on our understanding of progerin, compared with lamin A protein, progerin is shortened by 50 amino acids near the carboxyl terminus. This affects basic structure as well as post-translational processing of the pre-progerin protein. Progerin is permanently farnesylated, and is therefore associated with the inner nuclear membrane long-term.

Context of Use (COU) Considerations

Requestor's COU: *Pharmacodynamic/response biomarker to be used to assess efficacy of a drug intervention in future clinical treatment trials. It will be used to explore biological response related to an intervention, where the hypothesis will be that decrease in progerin levels can be reasonably expected to indicate disease.*

FDA's suggestions on COU for continued biomarker development: We will work with you to determine the most appropriate COU. We recommend that you address the following considerations:

3. Based on the analytical and clinical validation needed, we recommend that you consider and propose how progerin will be used as a pharmacodynamic biomarker for other possible COUs. For example, progerin may be used to provide proof-of-concept data to support future drug development by demonstrating a drug effect on a biomarker closely related to the pathophysiology of the disease, characterizing dose response, or confirming a proposed drug mechanism of action. In your future QP submission, please provide additional details on how progerin can be used as a pharmacodynamic biomarker or other type of biomarker category as defined by the FDA-NIH Biomarker Working Group Biomarkers, EndpointS, and other Tools (BEST, available at: <https://www.ncbi.nlm.nih.gov/books/NBK326791/?report=reader>). Provide information describing how the proposed analytical and clinical validation will support the COU. Please take into consideration the sample quality and validation requirement when drafting the COU for this biomarker.
4. To help refine the COU and determine the type of validation data that is needed to support the proposed COU, please inventory the samples in each clinical trial by two groups (with treatment and without treatment) and provide the following information:
 - a. The type of clinical samples that was collected (e.g., serum, plasma, or urine)
 - b. For each type of clinical samples, the total number of samples, the number of treatment-naïve and treatment-experienced patients, and the number of samples from each patient (mean, median, and range).
 - c. The duration (mean, median, and range) and condition of sample storage
 - d. Procedures that were used to collect and process the samples
 - e. Other available clinical information from patients from whom samples have been collected, such as demographics and concomitant trial medications.
5. We remind you that it is important to analyze your banked specimens only after the COU is refined, after the validation requirement of the progerin immunoassay is known, and after the validation experiments are complete.

To better understand the benefits of the identified biomarker as a DDT, and to continue to refine the COU, please provide the following information;

Analytical Considerations

6. Please note that you have the option to submit the progerin immunoassay for review in CDRH/OIR/DIHD. We recommend you first submit a pre-submission (Q-sub) that includes an outline of your analytical and clinical studies designed to support the Intended Use for your assay. For information on FDA Q-sub, please see FDA Guidance Document “The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance for Industry and Food and Drug Administration Staff” issued on September 29, 2017, link at <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>

7. We note that the Assay Development Report has not provided information regarding the accuracy as well as progerin stability during sample collection and handling, after short-term (bench-top at room temperature) and long-term (frozen at the intended storage temperature) storage. In your QP, please consider the type of analytical validation data that can be provided based on your samples and proposed COU. We recommend that you consider the following performance characteristics for the progerin immunoassay validation: accuracy, precision (repeatability and reproducibility), stability, linearity/recovery, quantitation limits (limit of detection, limit of blank, and limit of quantitation), and interference of the assay.
8. As there is no analytical well characterized reference assay available to verify assay performance, the assay performance can be defined in clinical terms including sensitivity and specificity. Please provide sensitivity and specificity for the assay.
9. Please provide a “Reference Range Study” to show progerin concentrations in normal healthy study subjects.
10. Please be clear in your QP what sample type will be used for the validation studies (e.g., serum, plasma, or urine).
11. We note that you intend to evaluate the stability of progerin protein over various storage times in mouse and human specimens. Describe how you will design your stability experiment to address the different short-term and long-term storage durations of the mouse and human specimens. Propose a study to show that the samples are still viable and have detectable levels of progerin protein after storage. Please also discuss how you propose to use the samples if your stability study shows that the progerin protein degrades over time. In the event that the stability experiment cannot provide data for all sample storage durations, describe how you would address data analysis for samples that are stored outside the stability limits. We can provide more specific guidance when additional data are available. Please refer to CLSI EP25-A “*Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.*”
12. You should determine the within-subject and between-subject variability of progerin levels in HGPS. This information would facilitate proper interpretation of progerin data resulted from clinical trials.
13. Please provide the Standard Operation Procedures (SOPs) on how the animal and clinical samples are collected, processed, and stored, and any other steps before the samples are analyzed. Provide as much detail about the different processes and SOPs. Identify any differences in the procedures and clarify if these differences would cause any variation in sample measurement and validation.
14. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical assay may be publicly posted if the biomarker is successfully qualified by the Agency. Please confirm technical parameters

and other pertinent information about the assay that may be made public to ensure the biomarker can be used as a drug development tool by any interested party. The biomarker qualification process does not endorse or qualify a specific assay for use with the biomarker.

Clinical Considerations

15. Please clarify whether the pathophysiology of progeria is attributable solely to the presence of progerin or if the absence of normal lamin A without the presence of progerin may be contributory to the progeria phenotype. Include references if possible.
16. You plan to evaluate progerin levels in mice and humans that have not received progeria-specific treatment. You will need to describe the methods used to identify untreated patients. Specifically, you should describe the data sources referenced to identify patients with progeria and detail the criteria and procedures used to select patients from these data sources for analysis. In interpreting the study results in mice and humans, we recommend that you take into consideration the sample collection timepoint (relative to age and treatment duration), duration of storage, assay variability, and patient characteristics.
17. You intend to evaluate the effect of progerin-targeted treatments on progerin levels in murine and human studies and hypothesize that drug treatment would result in the decrease of progerin levels. It is important to understand the time course of progerin reduction and assess whether the use of different sample collection timepoints relative to drug administration has an impact on the evaluation of progerin levels. The reduction in progerin may also vary as a consequence of combination therapy or use of single agents, some of which have different mechanisms of action and may affect progerin levels differently. In the absence of knowledge about the carryover effect of prior treatment on progerin concentrations, the relationship between the changes of progerin level after a change in therapy as evidence of effectiveness for a specific intervention need to be interpreted with caution.
18. If you plan to explore the correlation of progerin level/reduction with clinical outcomes after drug intervention, the clinical outcome measures must be standardized across subjects for the analysis results to be interpretable. Please also consider exploring the correlation of genotype and disease phenotype with progerin concentration or reduction.

Statistical Considerations

19. Please include a statistical analysis plan (SAP) in the QP submission. In your SAP, provide details including the generalized estimating equation linear regression with an unstructured covariance matrix to assess the relationship of progerin levels with age and gender. Please also consider whether the unstructured covariance matrix may cause a convergence problem.

You may designate a sequence of alternatives (in case of convergence failure) starting with the least parsimonious covariance structure and use a robust variance estimator, e.g. sandwich estimator. In addition, you proposed using data from two separate clinical trials to test the treatment effect. Please provide details including designs and statistical analysis plans of the two clinical trials.

20. One of your primary hypotheses is that plasma or serum progerin levels post lonafarnib treatment will be significantly decreased compared to baseline progerin levels pretreatment. Please provide references (if available) to clarify whether the putative decrease in progerin levels with lonafarnib treatment translates into a benefit in a clinical endpoint.
21. Your assessment of treatment effects is to compare post-treatment progerin levels to baseline progerin levels. Please note that there are many limitations to the ability of this approach to assess or confirm the treatment effects.

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) through email. We look forward to working with you on this beneficial project.

Sincerely,

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