BQP Qualification Program Cover Letter

Date: June 7, 2018

Subject: DDT QUALIFICATION SUBMISSION

DDT Type: Biomarker Qualification

ATTN: CDER-Biomarker Qualification Program

C/O CDER Document Room: Upon receipt notify:
CDER-BiomarkerQualificationProgram@fda.hhs.gov

Biomarker DDT Tracking Number: (in bold print), if previously assigned

Check Here	Submission Type
X	Letter of Intent
	Qualification Plan
	Full Qualification Package
	Update of Above (Check two, this box and one above)
	Other (please specify):

Biomarker Name(s): (in bold print) Identify the specific biomarker by name that is submitted for the specified stage of qualification. **progerin**

Context of Use: Describe the intended drug development use for the biomarker named above (1 to 2 sentences, see the graphic below for how to write the context of use.)

A COU is generally written to be consistent with the following structure:
[BEST biomarker category] to **[drug development use].**

The context of use will be the phamacodynamic/response category. Decreased progerin levels will be used to assess efficacy of a drug intervention in clinical treatment trials.

Contact Information: Complete contact information including name(s), affiliation, mailing address, email address, phone and fax numbers.

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BQP Qualification Program Cover Letter

Purpose Statement: Describe the purpose of the submission in 3-5 sentences.
The purpose of this submission is to request inclusion into the BQP for the certification of progerin as a biomarker for HGPS. Hutchinson-Gilford progeria syndrome (HGPS, Progeria) is a rare, fatal, premature aging disease caused by the protein progerin. Currently there is no validated biological biomarker for HGPS. We have developed a progerin assay that will be used to explore the biological response related to an intervention, where the hypothesis will be that decrease in progerin levels can be reasonably expected to indicate disease improvement.

Submission Statement: Include a statement in the cover letter that: "The physical media submission is virus free with a description of the software (name, version and company) used to check the files for viruses."

We are delighted to submit a Letter of Interest for Biomarker Qualification of the disease-causing protein, progerin, for assessing disease in the premature aging syndrome, Hutchinson-Gilford Progeria Syndrome. We have developed a sensitive, specific assay to measure this protein in biological specimens. The physical media submission is virus free. Symantec Endpoint Protection, Version 12.1.2015.2015, was used to check the files for viruses.

Additional Instructions for LOI/QP/FQP[1] submissions: For every electronic submission, a comprehensive table of contents should be submitted containing three or four levels of detail, with the appropriate bookmarks to key referenced sections in the document.

Table of Contents:

Included in this submission are the following PDF document files:

1. **Cover Letter**
2. **Letter of Interest**
3. **List of References**
4. **Summary of statistical plan to support this application**
5. **Assay Development Report**

[1] LOI: Letter of Intent; QP: Qualification Plan; FQP: Full Qualification Plan

Leslie B. Gordon, MD, PhD

Progerin Analysis Plan Synopsis
June 6, 2018
For FDA Biomarker Qualification Group

1. General summary

The intent is to use currently available progerin levels and outcome data, measured in children with Progeria and in mouse experiments, to assess the natural history of the disease-causing protein progerin, and assess the ability of progerin-targeted treatments to decrease progerin levels in plasma or serum. The plans for these analyses are outlined below (a more formal statistical analysis plan will be provided in the formal submission. The intent is to use progerin levels as a surrogate outcome in future clinical trials of intervention. If, in these future trials, intervention(s) is (are) shown to significantly lower progerin levels, then such results will be used to support approval of the intervention(s) for treatment of patients with Progeria.

Note that, currently, there is no intention to use progerin levels to create a patient classification tool; for example, there is no intention to establish a threshold or cutoff to classify patients as diseased and non-diseased.

2. Analyses of Mouse Data

Several studies have been undertaken on mice that express progerin and also display disease phenotypes similar to that of human disease in HGPS. Groups include no treatment, control treated, and various doses of several different treatments.

A. Progerin Stability: To test whether sample storage has effect on progerin levels, samples from similar mouse genotypes and with similar treatment (either no treatment, control treatment, or treated) but collected at different time points will be compared. Our hypothesis is that between equivalent mouse groups where samples have been stored for different periods of time will contain similar progerin.

B. Natural History: The untreated and control treated groups will be assessed for progerin levels with gender and age. Treatment groups will be compared with untreated groups for treatment effect on progerin levels.

C. For treatment analysis, the primary analyses of interest are the treated versus the control and untreated groups. The primary hypothesis for the mouse studies is that progerin will be decreased compared to control and untreated groups. Treatments include lonafarnib, RAD001, and RNA therapeutics. Secondarily, when possible, depending on the experiment, progerin levels will be compared with disease features such as vascular pathology or time-to-death, using Cox proportional hazards regression.

3. Analyses of Progerin levels in biological specimens from Children with Progeria

A. Progerin Stability: To test whether sample storage has effect on progerin levels in human specimens, samples from children with HGPS (either no treatment or treated) that were collected in a similar manner technically, but were collected in different years will be compared. Our hypothesis is that equivalent groups where samples have been stored for different periods of time will contain similar progerin levels, when adjusted for age and/or gender as is appropriate once gender and age analyses are completed (see below).

B. Natural History:

a) We will assess relationship of progerin levels with age and gender in untreated patients using generalized estimating equation linear regression, assuming an unstructured covariance matrix.

C. Treatment Effect: The primary hypothesis is that plasma or serum progerin levels will be significantly decreased with lonafarnib treatment vs. baseline untreated levels. There are two separate human clinical treatment trials that will be used for this testing. There will be no overlapping patients between these two trial groups. The first will be considered the exploratory group (N=25) [1], and the second will be considered the confirmatory group (N=36). Secondarily, the overall effect of lonafarnib treatment will be assessed by combining these two trial groups (N=61) [2].

D. Triple Therapy Assessments: In a clinical trial, children were treated with lonafarnib plus pravastatin plus zoledronic acid [3]. Overall the trial found that triple therapy was not beneficial over and above lonafarnib monotherapy, when examining pre-designed outcomes. Most patients were enrolled previously in the lonafarnib monotherapy trial (N=26) and some entered this trial without prior treatment (N=13). The effect of treatment will be assessed by comparing baseline progerin levels with on-therapy levels, separately and as one treatment group combined.

References

1. Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109: 16666-71.
2. Gordon LB, Shappell H, Massaro J, et al. Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. *JAMA : the journal of the American Medical Association*. 2018; 319: 1687-95.
3. Gordon LB, Kleinman ME, Massaro J, et al. Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. *Circulation*. 2016; 134: 114-25.