First Application of Computer-Assisted Analysis of Digital Photographs for Assessing Tophus Response: Phase 3 Studies of Pegloticase in Treatment Failure Gout

A. N. Maroli1, R. Waltrip1, M. Alton1, Herbert S. B. Baraf2, B. Huang1, C. Rehrig1 and R. Ford3,
Savient Pharmaceuticals, Inc., East Brunswick, NJ;2, Arthritis & Rheumatism Associates, P.C., Wheaton, MD;3RadPharm, Princeton, NJ

ABSTRACT

INTRODUCTION

Gout is a disease characterized in part by deposition of urate crystals in and around joints, producing tophaceous mass lesions that are visible, palpable, and measurable. Clinical studies have demonstrated the ability of pegloticase, a PEGylated recombinant uricase, to reduce or completely resolve tophi in patients with chronic gout refractory to conventional therapy. This was initially based on an adaptation of the principles of the Response Evaluation Criteria in Solid Tumors (RECIST)1 scoring criteria.

Methods and Scoring for Individual Measured Tophi

At Week 13, up to 5 tophi were selected per patient by the Central Reader for measurement, based on the availability of post-baseline photography. The first tophus on each side was selected, followed by additional tophi in a specific order. The reader then compared the post-baseline photographs with the baseline photograph of each selected target tophus, and the change in the areas of tophi from baseline to each subsequent visit was assessed. The change in the area of tophi from baseline was calculated using the method provided in the study protocol. The changes in the areas of tophi from baseline to each subsequent visit were then compared to the changes in the areas of tophi from baseline to the previous visit.

RESULTS

Treatment with the proposed clinical dose regimen of pegloticase 8 mg q2wks demonstrated reduction in tophus burden compared to placebo over time. At the first tophus response assessment visit at Week 13, 22% of subjects experienced complete response of at least one target tophus (p=0.011); after 6 months of pegloticase 8 mg q2wks treatment, 45% experienced CR (p=0.002). [Fisher’s exact test]

CONCLUSIONS

The CAPER method for tophus assessment was successfully included in two replicate multicenter, double-blind, placebo-controlled clinical trials, providing strong evidence of feasibility. Multiple investigators were able to perform the method with minimal crossover training using the CR paradigm. The CAPER method provides a method for tophus assessment that is both robust and consistent. The method for tophus assessment was successfully included in two replicate multicenter, double-blind, placebo-controlled clinical trials, providing strong evidence of feasibility. Multiple investigators were able to perform the method with minimal crossover training using the CR paradigm. The CAPER method provides a method for tophus assessment that is both robust and consistent.

REFERENCES


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METHODS (continued)

METHODS

Savient and RadPharm using imaging core laboratory, collaborated to develop an adaptation of standard methods for photographic tophus measurement. The vision of pegloticase for clinical trials was to standardize photography, measurement, and analysis of the method.

A protocol entitled “Chart for Independent Review of Tophaceous Gout Photographs” was created in parallel to detail all standardization procedures for photographic measurement, and analysis of the tophi.

A Board Certified Rheumatologist, familiar to study group was the independent central reader of the images. Electronic calipers, internally calibrated to the image using an embedded ruler, were used to determine the areas of tophi. Photographic images were read up to 2 tophi that were representative of the subjects tophus burden but which could not be accurately measured (e.g., due to location, shape or other factors) were also followed during the study. Unmeasured tophi had to be ≥10 mm at baseline in order for the reader to reliably assess changes in size.

Using the unmeasured tophi, were selected by the Central Reader for measurement. The first tophus on each side was selected, followed by additional tophi in a specific order.

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Pegloticase (CR) 100% decrease in the area of the tophus from baseline

Partial Response (PR): At least a 50% decrease in the area of the tophus from baseline

Stable Disease (SD): Neither a 50% decrease nor a 25% increase in the area of the measurable tophus can be demonstrated

Progressive Disease (PD): A 25% or more increase in the area of the tophus from Baseline.

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Method: unmeasured tophi were semi-quantitatively assessed by the central reader.

Scoring for Unmeasured Tophus: Individual categorical scores were determined for each target tophus

Complete Response (CR): 100% decrease in the area of the tophus from baseline

Imputed (I): An approximation of 50% or more reduction from baseline

Stable Disease (SD): Neither improvement nor progression from baseline can be demonstrated

Progressive Disease (PD): 50% or more increase in the area of the tophus

Subject’s Overall Tophus Response

• Best response reported among all target tophus (measurable and unmeasurable) for the subject, in the absence of new tophus or progression of non-target tophus or resolution of non-target tophus.

• Response categories include: Complete Response, Partial Response (including Marked Response and Improved), Stable Disease and Progressive Disease.

CAPER (Computer-Assisted Photographic Evaluation in Rheumatology) was created to provide categorical scoring of tophus response recorded by photographic imaging. Bi-dimensional measurements were considered to be more relevant for present application than a uni-dimensional approach. Tophi that were assessed were categorized as “measured” and “unmeasured” based on the Central Readers assessment of presence of distinguishable borders in the photographs.

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