Poster # 1111

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

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ABSTRACT

Purpose: Based upon anecdotal investigator-generated digital photographs that identified tophus elimination with pegloticase treatment in Phase 2, a standardized photographic and analytic process was developed to assess tophus response in 6-month, double-blind, placebo-controlled Phase 3 studies of pegloticase. **Method:** An approach to quantitation of tophus elimination was jointly developed by Savient and RadPharm. This used serial photography and a method of categorizing skin lesions similar to Response Evaluation Criteria in Solid Tumors (RECIST). As RECIST has been used by FDA/EMEA for oncologic drug approvals, the principles of RECIST were used to categorize the response of tophaceous mass lesions to a novel therapy. Specialized software for clinical trials was used to standardize image viewing, measurement, and annotation in an audit tracked environment for integrity of the central reading process. Method manual and site-based training programs were used to ensure standardization of equipment, image acquisition and quality assurance. Analysis and measurement of tophi were performed by an independent blinded Central Reader (rheumatologist). Investigational sites (n=56: US, Mexico, Canada) were trained using identical equipment and standard view templates for hands and feet. Quality procedures were used to assure that digital media were properly labeled, processed and delivered for image analysis. Assessment was blinded to and independent of any Sponsor or trial site input. From each subject's baseline views, Central Reader selected target tophi to follow utilizing a "Sequential Locked Read" paradigm; post-baseline photographs were read and compared with baseline image with no knowledge of future assessments. Calibrated electronic calipers were used to measure the tophus area. Complete response (CR) of an individual target tophus was defined as 100% decrease in area. Overall tophus response per subject was the complete resolution of at least one tophus without appearance of a new tophus or progression of an existing tophus. **Results:** Method captured tophus response and was successfully operationalized in a multicenter clinical trial. Treatment with intravenous pegloticase 8 mg q2 weeks led to reduction in tophus burden compared to placebo: 22% of subjects experienced CR of a target within first 3 months (p=0.011) and 45% within 6 months (p=0.002). **Conclusion:** Computer-assisted analysis of digital photographs, used for skin lesions in oncology, has been successfully applied to assessment of tophus treatment response in rheumatology. Standardized photographic data recording and computer-aided analysis in a Central Reader paradigm, successfully documented outcomes, with findings consistent with clinical observations. **Keywords:** clinical trials, gout and outcome measures
Disclosure: A. N. Maroli, Savient Pharmaceuticals, Inc., 3; **R. Waltrip**, Savient Pharmaceuticals, Inc., 3; **M. Alton**, Savient Pharmaceuticals, Inc., 3; **H. S. B. Baraf**, Savient Pharmaceuticals, Inc., 9; **B. Huang**, Savient Pharmaceuticals, Inc., 3; **C. Rehrig**, Savient Pharmaceuticals, Inc., 3; **R. Ford**, RadPharm, 9.

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 observed anecdotally in photographs from a Phase 2 clinical study of pegloticase, leading Savient to develop a photographic method to document resolution of tophi during two replicate double-blind, placebo controlled Phase 3 studies, since standard methods for tophus assessment did not exist. This method was acceptable to the FDA.

Serial photographic assessment of lesions is a component of Response Evaluation Criteria in Solid Tumors (RECIST) and has provided mechanisms for health authority approval of cancer treatments. The analogy of oncologic skin lesions with tophaceous mass lesions provided a basis to develop a similar approach for assessing tophus response.

Systems and procedures were developed for the assessment of the reduction in tophus burden. The key components of this methodology, referred to as **CAPER** or Computer-Assisted Photographic Evaluation in Rheumatology, included

- Standardized digital photography
- Computer assisted measurement and analysis of tophi by an independent reviewer
- Blinded Central reader paradigm

The ability of this method for computer-assisted analysis of digital photographs to quantify reduction in tophus size was used in the Phase 3 studies in order to demonstrate its feasibility as a research tool.

METHODS

Savient and RadPharm, an imaging core laboratory, collaborated in the development of standardized methods for photographing gout tophi for use in Phase 3 clinical studies of pegloticase. Assessment of the effect of pegloticase or placebo intervention on tophus size was based on an adaptation of the principles of the Response Evaluation Criteria in Solid Tumors (RECIST1)[1] scoring criteria.

A study protocol entitled "Charter for Independent Review of Tophaceous Gout Photographs" was created in parallel to detail all aspects of the standardized processes for photography, measurement, and analysis of tophus burden.

A Board Certified Rheumatologist, blinded 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 using a Sequential Locked Read paradigm.

Post-baseline photographs were read independent from site or sponsor personnel input and compared with the baseline photograph without knowledge of future assessments. RadPharm software was used for electronic measurement and document management of the electronic images.

At baseline for the Phase 3 studies, photographs were taken of hands and feet for all patients, regardless of presence of tophi, and up to two other anatomic locations with tophi. These were repeated with the same views at all subsequent assessments. Hard copy printouts of each photograph were mailed to the investigational sites for consistency of patient positioning in subsequent photographs.

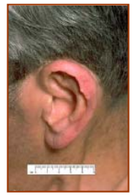
Photographs were transported to RadPharm on electronic media (i.e., memory card) and upon receipt underwent quality control assessment for both image quality and consistency with protocol requirements and established standards.

METHODS (continued)

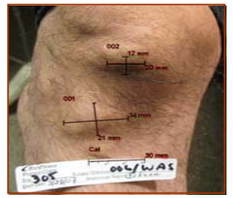
Investigator Site: Standardized Equipment and Resources

- Camera (calibrated and preset) and media card
- Light stand and lights
- Preprinted templates for placing hands and feet in standard positions
- Preprinted ruler labels
- Training manual and video

Light Stand with camera and template for hands and feet.



Calibration rulers used for anatomic sites other than hands and feet



Photos show the use of electronic calipers measuring the two longest diameters of measured tophi (perpendicular lines) and the ellipse designates a tophus at the DIP joint with indistinguishable borders

CAPER (**C**omputer-**A**ssisted **P**hotographic **E**valuation in **R**heumatology**)** 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.

Methodology and Scoring for Individual Measured Tophi

- At baseline, up to 5 measureable tophi in the photographs were chosen by the Central Reader for measurement over the course of pegloticase therapy. To be considered measurable, tophi had to be ≥ 5 mm in the longest dimension, and had to have distinguishable borders.
- Central Reader identified tophus margins and placed the electronic calipers at the edges of the longest diameter.
- Central Reader identified margins of the longest perpendicular diameter and placed the electronic calipers at the edges.
- Computer measured the length of the two diameters and calculated the area.

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

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

Marked Response (MR): At least a 75% 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.

Methodology and Scoring for Individual Unmeasured Tophi

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 approximately ≥ 10 mm at baseline in order for the reader to reliably assess changes in size.

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): Disappearance of the tophus

Improved (I): An approximate 50% or greater reduction from baseline

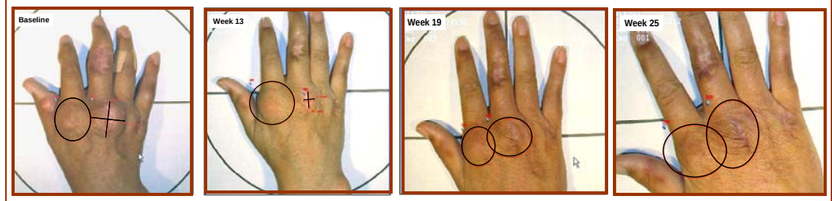
Stable Disease (SD): Neither improvement nor progression from baseline can be determined

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

Subject's Overall Tophus Response

- Best response reported among all target tophi (measureable and unmeasured) for the subject, in absence of progressive disease of an individual tophus or development of a new tophus.
- Response categories include: Complete Response, Partial Response (including Marked Response and Improved), Stable Disease and Progressive Disease.

RESULTS



Photographs of the same hand at Baseline, Week 13, Week 19, and Week 25 of pegloticase 8 mg every 2 weeks. Note that the two target tophi at the MCP joints have completely resolved by Week 19, as have all observed non-target tophi. Week 25 is a close-up to optimally demonstrate complete resolution.

Assessment of Overall Tophus Response in Tophus Evaluable Subjects Uric acid Responder vs Non-Responder Final Visit, n (%)

	Pegloticase 8 mg				
	q2wks [N=62]		q4wks [N=64]		Placebo
	Responder N=25	Non-Responder N=37	Responder N=28	Non-Responder N=44	Non-Responder N=29
CR	13 (62)	8 (26)	7 (41)	4 (11)	2 (7)
PR	4 (19)	8 (26)	6 (35)	6 (17)	6 (22)
SD	4 (19)	10 (32)	1 (6)	20 (57)	13 (48)
PD	0 (0)	5 (16)	3 (18)	5 (14)	6 (22)
Tophus Evaluable Subjects (n)	21	31	17	35	27

* < 6 mg/dL at least 80% of time during months 3 and 6, combined

Treatment with the proposed clinical dose regimen of pegloticase 8 mg q2 weeks 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 a 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 international clinical studies, providing strong evidence of feasibility. Multiple investigators were able to perform the method with minimal a training program. Data capture using digital images and rating by a rheumatologist supports the validity of the method. Tophus response results paralleled both the treatment regimen assignments and the uric acid response, which supports the construct validity of the method.

Limitations of **CAPER**

1. Reader uses a two dimensional image of a three dimensional lesion compared to direct clinical observation.
2. Difficulty to identify borders of resolving lesions. Standard employed in this work was focused on complete resolution.
3. Method does not allow ascertainment of firmness of tophi, which may be considered to be relevant to the rate of tophus resolution with urate-lowering therapy

Although central readers have the disadvantage of being removed from the clinical situation, use of a Central Reader paradigm **CAPER** has the advantage of reducing reader variance over direct measurements at multiple investigational sites. It also creates a source of primary data (digital photographs) which can be subsequently reanalyzed using the same software application for confirmatory or supplemental analyses.

The feasibility of **CAPER,** demonstrated in this study by the tophus response to pegloticase therapy, suggests that this method may be broadly adapted across multiple rheumatologic conditions e.g., psoriatic disease and rheumatoid arthritis.

References

1. Therasse P, Arbuck S, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumours. J Natl Cancer Inst 2000;92:205–16

Presentation # 1111.
Presented at the ACR/ARHP Annual Scientific Meeting, October 17-21, 2009, Philadelphia, PA.
Research sponsored by Savient Pharmaceuticals, Inc

RADPHARM The Imaging Core Lab