

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208054Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ADDENDUM

NDA/BLA Serial Number: 208054

Drug Name: Fluciclovine (18F)

Indication(s): Biochemically recurrent (BCR) prostate cancer (proposed)

Applicant: Blue Earth Diagnostics Ltd

Date(s): Submitted to FDA: 9/28/2015
PDUFA date: May 27, 2016

Review Priority: Priority

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Anthony Mucci, Ph.D. (Primary reviewer)
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Concurring Reviewers: Thomas Gwise, Ph.D., Deputy Division Director

Medical Division: Division of Medical Imaging Products

Clinical Team: Phillip Davis, MD (Primary clinical reviewer)
Nushin Todd, MD (Clinical Team Leader)

Project Manager: Thuy Nguyen

Keywords: Modified Sensitivity, Positive Predictive Value, Agreement, Subject based.

Executive Summary - Addendum

This reviewer regrets depending on the applicant's study report with a transcription error and writing the following sentences in the secondary statistical review, which are wrong:

In these re-analyses (BED001), among the 13 subjects (not counting any subject twice) with false positive or false negative images, 9 belonged to a category $PSA \leq 1.05$. These data suggest that fluciclovine (18F) imaging performance may not be reliable among subjects with lower blood PSA levels.

The seemingly correct version (not verified by the primary statistical reviewer) is as follows:

*In these re-analyses (BED001), among the 18 subjects (not counting any subject twice) with false positive or false negative images, 5 belonged to a category $PSA \leq 1.78$ ng/mL. These data **may** suggest that fluciclovine (18F) imaging ~~performance~~ may not be reliable among subjects with lower blood PSA levels.*

Relationship between PSA and fluciclovine images

In patient population with rising PSA levels, recurrent prostate cancer is likely to occur. A potential weakness of fluciclovine imaging in this patient population is that at low end of the PSA scale, it seems to give erroneous results (false negatives and false positives) and may be less useful, although that is not statistically evident from the data that the applicant collected and reported. This part of the re-analyses is post-hoc and any inference made through multiple testing and method selection is subject to inflated type-I error probability. Hence the confidence level is hard to interpret.

The clinicians tend to report descriptive information regarding PSA levels and imaging execution in the label (e.g. Axumin label) from safety perspective based, not on statistical rigor, but on trends, history with previous imaging products, and biologic plausibility. This component of labeling is acceptable to this reviewer.

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/s/

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Keywords: Modified Sensitivity, Positive Predictive Value, Agreement, Subject based.

EXECUTIVE SUMMARY

Fluciclovine (18F) is a diagnostic radiopharmaceutical for positron emission tomography (PET) imaging to visualise increased amino acid transport that occurs in malignant tumors. It is not metabolized, nor is it incorporated into newly synthesized proteins. PET imaging studies have demonstrated that fluciclovine (18F) is preferentially taken up into prostate cancer and glioma compared with surrounding normal tissue and that visualization of the image is not obscured by bladder uptake.

Many subjects treated with curative intent following a diagnosis of primary prostate cancer experience disease recurrence. In a vast majority of cases, evidence of recurrent disease is based on serial measurement of prostate specific antigen (PSA) alone. This is often referred to as biochemically recurrent (BCR) prostate cancer. In subjects with BCR prostate cancer, it is critical to determine the location of the recurrence, as this defines the optimal choice of therapy. The diagnostic accuracy of standard imaging tests for the identification of sites of recurrence is low; almost 90% of the standard battery of imaging tests, including CT/MRI and bone scintigraphy, may be negative and therefore more accurate, non-invasive imaging techniques for the detection of recurrent prostate cancer are needed. The use of fluciclovine (18F) PET is to identify sites of recurrence of prostate cancer in subjects with suspected recurrence based on rising PSA post therapy.

This New Drug Application (# 208054) is primarily a retrospective evaluation of subjects who have had therapy for primary prostate cancer and have met an inclusion criterion of rising PSA, which is suggestive of cancer recurrence. Two studies were conducted by two universities, namely, Emory University and University of Bologna for fluciclovine (18F) to detect sites of prostate cancer recurrence. Emory Study (R01), conducted at Emory University, which issued in a publication: Schuster et al, Journal of Urology, Volume 191, May 2014. Bologna Study, conducted at the University of Bologna, which issued in the publication: Nanni, et al, Clinical Nuclear Medicine, 2015. The Applicant (Blue Earth Diagnostics, Ltd) acquired the rights to the data from these two studies, in order to re-evaluate the relevant data. This application is a submission of those re-analyses (BED001 and BED002). One significant limitation of such re-analyses is that the applicant already knew the results including the histological standard of truth (SOT). This applicant seems to be cautious of that fact while conducting re-analyses BED002 using three expert readers who were blinded to all the clinical information (including SOT) upon FDA's recommendations. One should still use extreme caution while evaluating this application in terms risk-benefit considerations (please see the clinical review(s)). From statistical point of view, there were no significant safety issues, no deaths or serious adverse events related to fluciclovine (18F) reported and evaluation of efficacy is given below.

Re-analyses BED001 and BED002 for Emory Data:

The investigation of recurrence, which is the primary objective of Emory data for studies BED001 and BED002, consists of SOT evaluation of lesions detected through test images, control images, and other techniques or agreement measures between test images and control images. Since patient management is largely dependent on whether recurrence is limited to the prostate/bed or is additionally or exclusively outside this area (extra-prostatic), the lesion

detections are assigned a location, (prostate/bed; extra-prostatic), and test efficacy then consists of correctly evaluating recurrence for these two regions, and at subject level. (Note: Subject is recurrent if and only if a region shows metastases.)

The patient population included were, as expected, elderly (mean age 66.6, median age 67 years). Approximately 19% of the group was African american, the rest being predominantly white. PSA values prior to scan ranged from 0.05 to 44.76ng/mL (mean 5.96, median 2.92 ng/mL). PSA doubling time (PSA-DT), where calculable (N=98), averaged 12 months (median 8.69 months). All patients had negative bone scans prior to fluciclovine imaging. Fluciclovine PET-CT images were read by a number of trained nuclear medicine fellows on site. The results of the scans and of biopsy analyses were available to the team during the study period.

For the SOT, and at subject level: If all lesions gathered through biopsies and evaluated by histopathology are negative, the subject has disease negative status for the primary analyses. The critical element here is that there is no SOT that evaluates the subject’s status independently of histology evaluations of lesions detected by test, control, and other images or methods that direct biopsies. Therefore it is not possible to measure the standard performance characteristics (sensitivity and specificity) of fluciclovine (18F). The applicant chose Positive Predictive Value (PPV) as the primary endpoint, which can be defined at several levels – lesion/region/subject. Here the stat team chose the subject level as the critical and clinically meaningful level relevant to efficacy considerations. The primary reviewer has focused on two measures at subject level, namely PPV and modified sensitivity, for the following reasons: (1) PPV is the applicant’s primary endpoint (which is affected by prevalence of 70% in this study), (2) Some measure that acts as a corrective to the Stand-Alone of PPV is necessary, and modified sensitivity is meaningful here, defined as *proportion among patients with SOT Positive lesions who were SOT positive for fluciclovine (18F)*. The main observed results are given in following table.

Table 1: Results for Emory data (lower limits of 97.5% one sided confidence interval for PPV verified by primary statistical reviewer are given in the parenthesis)

	On site (un-blinded) BED001	Blinded Reader 1 BED002	Blinded Reader 2 BED002	Blinded Reader 3 BED002
N* (# of subjects)	105	103 (2 indeterminate)	104 (1 indeterminate)	98 (7 indeterminate)
True Positive	73	74	71	62
False Positive	19	24	23	13
True Negative	12	5	7	15
False Negative	1	0	3	8
PPV	79% (71%)	76% (67%)	76% (67%)	83% (74%)
Modified Sensitivity	99%	100%	96%	89%

*: Six subjects were counted twice for 2 administrations of the test drug.

In these re-analyses, among the 13 subjects (not counting any subject twice) with false positive or false negative images, 9 belonged to a category $PSA \leq 1.05$. These data suggest that fluciclovine (18F) imaging performance may not be reliable among subjects with lower blood PSA levels.

Re-analyses BED001 and BED002 for Bologna Data:

The applicant has collected subject level data from a total of 88 subjects recruited into the C11-choline comparison study at Bologna University into the BED-001 (and BED-002) database. Several of these subjects underwent repeat scans giving a total of 96 scan pairs for analysis. As this is a within subject dataset, there is complete overlap of subject demographic features in this group. All except 3 subjects had undergone previous radical prostatectomy with or without adjuvant radiotherapy. Subjects were white males, mean age ~67 years with a PSA at time of scan ranging from 0-22.72ng/mL (mean 2.9; median 1.44ng/ml). PSA-doubling time (PSA-DT), where calculable (N=70) averaged 6.43 months (median 2.73 months). Subjects enrolled at this site also underwent PET-CT using C11-choline within 1 week of the fluciclovine PET-CT scan. Scans were read by a number of fellows, previously trained in the use of C11-Choline PET-CT on site.

The primary outcome in this assessment is a within subject comparison of agreement/concordance between the on-site fluciclovine PET-CT and 11C-Choline PET scan reads (BED001) assessed using Cohen's Kappa = 0.62 (95% CI 0.48, 0.76), whereas blinded reads (BED002) of fluciclovine PET-CT (and C11-Choline reads) gave Cohen's Kappa values 0.32, 0.42 and 0.53. The raw agreement values of on-site reads and 3 blinded reads are 78%, 61%, 67% and 77% respectively. There was a "spread" in agreement between blinded and on-site reads (61% to 78%). The applicant justified this spread by calling Bologna images difficult to read. These are applicant's results and NOT verified by the primary statistical reviewer.

In totality, the evidence supports the efficacy of fluciclovine (18F) for biochemically recurrent prostate cancer. As mentioned above, one should carefully look at risk-benefit considerations for this product and [REDACTED] (b) (4)

[REDACTED] The indication should be restricted to identification of potential sites of prostate cancer recurrence (based on elevated PSA levels) for subsequent histological findings for patients who have non-informative imaging tests, including CT/MRI and bone scintigraphy.

Jyoti Zalkikar

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA NDA 208054

Drug Name: 18F-Fluciclovine

Indication(s): PET Imaging for Detection of Prostate Cancer Recurrence

Applicant: Blue Earth Diagnostics

Date(s): Submission Date: 9 / 28 / 2015
PDUFA Date: 5 / 27 / 2016

Review Priority: Priority Review

Biometrics Division: DBV

Statistical Reviewer: A G Mucci, PH. D.

Concurring Reviewers: Jyoti Zalkikar, PH. D. (Secondary Reviewer)
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Medical Division: Division of Medical Imaging

Clinical Team: Medical Reviewer: Phillip Davis MD

Project Manager: Thuy Nguyen

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1 EXECUTIVE SUMMARY

NDA208054 is a submission consisting of retrospective analyses and re-analyses of data from several sources, primarily the following two:

Emory Study (R01), conducted at Emory University, which issued in a publication (Schuster et al, Journal of Urology , Vol 191, May 2014).

Bologna Study , conducted at the University of Bologna, which issued in the publication (Nanni, et al, Clinical Nuclear Medicine, 2015)

The Sponsor (blue earth) acquired the rights to the data from these two studies, and from several other sources, in order to re-evaluate the relevant data , in support of a claim for the Efficacy of their diagnostic 18 F (FACBC) PET, hereafter referred to as Axumin, or Fluciclovine PET, (or simply Fluciclovine), in detection of recurrent prostate cancer.

The proposed Indication is:

Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence. (b) (4)

(b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4).

The Primary Objective is:

To demonstrate that Fluciclovine PET imaging is useful in the detection of metastatic lesions in patients who had been previously treated for primary prostate cancer and whose PSA profile, two years or more post-treatment (surgery/radiation, etc) is consistent with disease recurrence.

Evaluations relevant to this Indication require a Standard of Truth (SOT). The only data source determined to have an SOT for the primary statistical analyses the Emory Study, which provided both a Comparator diagnostic (Proscint) and histological confirmation for image findings. One significant limitation on the Emory results was the absence of blinded reads of the data. The Agency therefore recommended to the Sponsor that the retrospective analyses be supplemented by blinded reads of both the Fluciclovine images and the Proscint images from the Emory Study. This recommendation was implemented through blinded reads conducted at the University of Bologna. Consequently, the focus exclusively of this Review will be the Evaluation of Efficacy for the Test Diagnostic (Fluciclovine PET) through standard Performance Characteristics for detection of prostate cancer recurrence, in the following sense:

- (a):Patients with Fluciclovine lesion detections have a high probability of having some or all of these lesions determined as Positive by histology
- (b): Patients with histology Positive lesions have a high probability of having had some or all of these lesions detected by Fluciclovine

Evaluation of the Efficacy Criteria (a) and (b), as applied to the On-Site and blinded reads of the Emory data, are the focus of this review. The Reviewer's conclusion is that the results support the Efficacy claim.

2 INTRODUCTION

2.1 Overview

This NDA Study is primarily a retrospective evaluation of patients who have had therapy for primary prostate cancer and have met an inclusion criterion of rising PSA, which is strongly suggestive of cancer recurrence. The investigation of recurrence, which is the primary objective of the investigation, consists of histological (SOT) evaluation of lesions detected through Test Images, Control Images, or other techniques. Since patient management is largely dependent on whether recurrence is limited to the Prostate/Bed or is additionally or exclusively outside this area

(Extra-Prostatic), the lesion detections are assigned a location, (Prostate/Bed; Extra-Prostatic), and Test Efficacy then consists in correctly evaluating recurrence for these two regions, or at patient level.(Note: Patient is recurrent iff a region shows metastases.)

For the SOT, and at Patient Level: If no lesions gathered through biopsies and evaluated by histopathology are Positive, the patient has disease Negative status for the Study's primary analyses. If any such lesion is Positive for histology, then the patient is Positive for recurrence. Likewise, the histological status of lesions in the two regions singled out above determine the Standard of Truth status for those regions. The critical element here is that there is no SOT that evaluates the patient's status independently of histology evaluations of lesions detected by Test, Control, or other images or methods that direct biopsies.

The principal retrospective analyses conducted by the Sponsor were dedicated to the evaluation of Diagnostic Performance measures, such as Positive Predictive Value (PPV), Sensitivity, etc. The Sponsor's primary study is titled BED-001, and was based exclusively on data provided by an Emory Study (Study R01), whose principal results were published in Schuster et al, Journal of Urology, 2014. This review will concentrate almost exclusively on the Sponsor's Study BED-001, the exception being the addition of analyses of blinded read results of the Emory data conducted, under Sponsor direction, at the University of Bologna.

A large number of detected lesions (371), gathered from these several Imaging sources, along with other biopsied lesions not directed by images, underwent histological evaluation. In broad terms, the Study Objective was to establish that the Test Modality, on its own, provided Efficacy with respect to Subject and Region classifications for disease recurrence. In addition to these patient and Region efficacy evaluations, a lesion level evaluation was also conducted, but is considered to be of secondary interest.

Formally:

NDA208054 is a retrospective study of data acquired by the Sponsor (blue earth) from several existing sources (principally four), only one of which – the Emory Study – provided elements adequate for and consistent with evaluations relevant to the Sponsor's Primary Efficacy Objective, which was to demonstrate that Fluciclovine PET imaging was useful in the following sense:

Primary Efficacy Objective

Fluciclovine PET imaging is useful in the Detection of metastatic lesions in patients who had been previously treated for primary prostate cancer and whose PSA profile, two years or more post-treatment (surgery/radiation), signaled disease recurrence.

Study Design Overview**BED-001 Objectives and Design (Source data R01)**

Title: A Retrospective Observational Study Investigating the Safety and Effectiveness of Fluciclovine (F-18 FACBC) PET Ligand in Human Subjects.

Primary Efficacy Objective (Clinical Study Report September 2015):

To evaluate the ability of Fluciclovine PET-CT Imaging to detect recurrence of prostate carcinoma in the prostate bed validated by pathological analysis of prostate bed biopsies and patient follow-up.

Principal Inclusion Criterion: Patients had been previously treated for localized prostate carcinoma (usually by prostatectomy and/or radiation) at least two years before entry into the Study, and were currently suspicious for disease recurrence (metastases) based on rising PSA.

Population for Primary Analyses: (EAS: Efficacy Analysis Set):

Patients had Fluciclovine PET-CT Imaging and had at least one lesion detected, by any means, for which an adequate histology report (Positive/Negative for disease) was acquired .
A total of 105 Emory patients provided Standard of Truth (SOT) data.)

Primary Levels of Analysis**Region Level Analysis:**

A region ({Prostate/Bed or Extra-Prostatic) is Positive for the SOR if at least one lesion detected in the region is validated by histology as Positive ; Negative if all detected lesions are histology Negative. If a region provides no detections, it is removed from the region level analyses. Given this SOT Region level population, performance statistics for the Test are:

Sensitivity = Se(Test) = Proportion of Test Positive Regions among all Positive Regions

Specificity = Sp(Test) = Proportion of Test Negative Regions without Fluciclovine detections

Note here that all Test detections are classified as Positive.

Subject Level Analysis

The subject is Positive for the SOR if at least one lesion detected in the subject is validated by histology as Positive ; Negative if all detected lesions are histology Negative. If a subject provides no detections, he is removed from the subject level analyses. Given this SOT subject level population, Sensitivity for the Test at Subject Level is:

Se(Test) = Proportion of Test Positive Subjects among all SOT Positive Subjects

Sp(Test) = Proportion of SOT Negative Subjects without Fluciclovine detections

Primary Endpoint

The Sponsor's Primary Endpoint is Positive Predictive Value (PPV). This Endpoint can be defined at several levels – lesion/region/subject. Thus, for any level, call it Level L:

PPV = Proportion of SOT Positives at Level L among Fluciclovine detections at Level L

Thus, for instance:

Subject PPV=Proportion of SOT Positive Subjects among Fluciclovine Positive Subjects

Primary Statistical Objective

The Primary Statistical Objective is to demonstrate that, for the Prostate/Bed Region:

(*): Success Criterion (*) PPV > .50 (Chance)

Additional Note: In order that Fluciclovine be validated as a True Positive at, say, Subject Level, it is not enough that the subject be SOT Positive for some lesion found by some modality, and that Fluciclovine make at least one detection. Rather, at least one of the SOT Positive lesions had to be detected by Fluciclovine.

Study Primary Results

The primary results at the Prostate/Bed level are presented in the table below. The original Emory On-Site read is compared to the three blinded Bologna reads. Note that PPV > 50% is achieved by all readers, as established by the Lower Limit of the one-sided CIs. Since PPV as a Stand-Alone addresses the levels at which the Test correctly predicts metastases, but not how often it misses metastases, the Reviewer calls attention to Sensitivity as a potential companion statistic. Note that the Sensitivity (SE) is very high for all but the third blinded reader.

Table(1):Prostate/Bed (Parentheticals () contain Lower limits of 97.5% One-Sider CIs)

	On -Site	RDR1	RDR2	RDR3
N (Regions)	97	98	97	96
TP	57	58	56	47
FP	27	29	26	15
TN	12	10	12	24
FN	1	1	3	10
SE	98% (94%)	98% (95%)	95% (91%)	83% (73%)
SP	31% (16%)	26% (12%)	32% (17%)	62% (51%)
PPV	68% (58%)	67% (57%)	68% (58%)	76% (65%)
NPV	92% (77%)	91% (73%)	80% (60%)	71% (55%)

The primary results at the Subject level Prostate/Bed level are presented in the table below. The comments relevant to the Prostate/Bed table above apply here also.

Table(2): Subject Level (Parentheticals () contain Lower limits of 97.5% One-Sider CIs)

	On -Site	RDR1	RDR2	RDR3
N (Subjects)	105	103	104	98
TP	73	74	71	62
FP	19	24	23	13
TN	12	5	7	15
FN	1	0	3	8
SE	99% (97%)	100%	96% (91%)	89% (83%)
SP	39% (19%)	17% (3%)	23% (8%)	54% (35%)
PPV	79% (71%)	76% (67%)	76% (67%)	83% (74%)
NPV	92% (77%)	100%	70% (40%)	65% (45%)

Overall Conclusions

The Reviewer concludes that Fluciclovine Efficacy has been established.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Tables and data sets were adequate for purposes of the review.

3.2 Evaluation of Efficacy

The focus in this NDA is on patients who have had therapy for primary prostate cancer and whose condition at time of study inclusion is consistent with cancer recurrence, as suggested primarily by rising PSA. The principal concerns are validation of recurrence and also location of recurrence, since location is directly linked to patient management. Although the sites for recurrence are many, a rough partition of the anatomy into two regions: Prostate/Bed and Extra-Prostatic (here signaling everything outside the Prostate/Bed) is adequate for review purposes.

Recurrence, in the context of this review, is established through histological validation that biopsied lesions are disease positive. If no lesions gathered and evaluated by histopathology are Positive, the patient has disease Negative status for the Study's primary analyses, although secondary methods for establishing disease recurrence, such as patient Follow-Up, could change patient status from Negative to Positive. However, within the confines of this Review, patient status will be determined solely on the basis of histology results for lesions.

Several imaging modalities were employed for lesion detection in this Study: MRI, PET, SPECT, Ultrasound, etc, and there were also random biopsies that provided lesions. The Imaging modality under evaluation (Test Imaging Modality) was Fluciclovine PET-CT. A large number of detected lesions (371), gathered from these several sources, underwent histology evaluation. In broad terms, the Study Objective was to establish that the Test Modality, on its own, provided Efficacy with respect to patient classifications for disease recurrence. Efficacy evaluations were carried out on three levels: Lesion/Region/Patient.

The statistics dedicated to the Efficacy analyses were are of the standard variety: Sensitivity/Specificity, Predictive values, etc, all of which require a Standard of Truth for their evaluation. So it is important to recognize here that the Standard of Truth (SOT) employed in this Study, namely binary classifications (at lesion/Region/Patient levels), as determined by lesion histology for lesions detected by one or more Imaging modalities, is entirely dependent on the means used to acquire these lesions, and this implicates the Test Modality in Verification Bias to some degree. That is, Fluciclovine PET could significantly determine part of the Truth involved its own validation through the population of lesions it itself provides for histology. This would be especially so if most lesions were detected solely by Fluciclove PET-CT. This scenario is not unusual in Medical Imaging studies, but it does require highlighting. In any event, it should be understood that Sensitivity/Specificity, etc are used here as names for something that they aren't, but no obvious alternative names recommend themselves at the present moment. (Maybe something like Positive Detection Rate, or Conditional Sensitivity could substitute for Sensitivity.)

Overview

NDA208054 is a retrospective study of data acquired by the Sponsor (blue earth) from several existing sources (principally four), only one of which – the Emory Study – provided elements adequate for and consistent with evaluations relevant to the Sponsor's Primary Efficacy Objective, which was to demonstrate that Fluciclovine PET imaging was useful in the following sense:

Primary Efficacy Objective

Fluciclovine PET imaging is useful in the Detection of metastatic lesions in patients who had been previously treated for primary prostate cancer and whose PSA profile, two years or more post-treatment (surgery/radiation), signaled disease recurrence.

The principal retrospective analyses conducted by the Sponsor were dedicated to the evaluation of Diagnostic Performance measures, such as Positive Predictive Value (PPV), Sensitivity, etc, which required a Standard of Truth (SOT). The Sponsor's primary study is titled BED-001, and was based exclusively on data, and largely on the previous analyses, provided by an Emory Study (Study R01), whose principal results were published in Schuster et al, Journal of Urology, 2014. This review will concentrate almost exclusively on the Sponsor's Study BED-001, the exception being the addition of analyses of blinded read results of the Emory data conducted, under Sponsor direction, at the University of Bologna. A brief overview of the study design features relevant to the primary efficacy evaluations is presented directly below.

Study Design Overview

BED-001 Objectives and Design (Source data R01)

Title: A Retrospective Observational Study Investigating the Safety and Effectiveness of Fluciclovine (F-18 FACBC) PET Ligand in Human Subjects.

First Version of Primary Efficacy Objective (Protocol November 2014): To investigate the Effectiveness of Fluciclovine PET Imaging used as an Adjunct to existing management in patients with primary or suspected recurrence of prostate cancer

Second Version of Primary Efficacy Objective (Clinical Study Report September 2015): To evaluate the ability of Fluciclovine PET-CT Imaging to detect recurrence of prostate carcinoma in the prostate bed validated by pathological analysis of prostate bed biopsies and patient follow-up.

Principal Inclusion Criterion: Patients had been previously treated for localized prostate carcinoma (usually by prostatectomy and/or radiation) at least two years before entry into the Study, and were currently suspicious for disease recurrence (metastases) based on rising PSA.

Primary Endpoints/Analyses

Version#1 for Population for Primary Analyses: (EAS: Efficacy Analysis Set):

Patients had Fluciclovine PET-CT Imaging and had at least one lesion detected on Fluciclovine Images that provided an adequate histology report (Positive/Negative for disease.) A total of 105 Emory patients provided Standard of Truth (SOT) data.)

Note#1: The Reviewer believe this characterization of the EAS to be incorrect. A characterization consistent with the contents of the Primary Data Set (ADLES) is:

Version#2 for Population for Primary Analyses: (EAS: Efficacy Analysis Set):

Patients had Fluciclovine PET-CT Imaging and had at least one lesion detected, by any means, for which an adequate histology report (Positive/Negative for disease) was acquired A total of 105 Emory patients provided Standard of Truth (SOT) data.)

Primary SOT: The statistics relevant to primary analyses were ultimately based on biopsied lesions with definitive histology reports (Positive/Negative for disease). These lesions were detected by one or more among several alternative imaging modalities: Ultrasound, MRI, CT, bone scans, etc, but, with one exception(additional to Test Images), none among these was required, and therefore the number of patients with, say, Ultrasound, could constitute a small percentage of the EAS. The single exception was ProstateScint SPECT Imaging, which was used as a Comparator in Study R01, but which was not featured as an element relevant to BED-001 primary analyses.

Levels of Analysis: There were several levels of statistical analysis of the data: lesion level, region level, subject level. These will be described in detail belowThe critical feature common to all these levels is their ultimate dependence on lesion results.

Lesion Level: The SOT defaults to the total collection of lesions with histology validation as Positive or Negative. These lesions could have been detected by any imaging modality. Given this SOT population, Fluciclovine Sensitivity at Lesion Level would be:

Se(Test) = Proportion of Fluciclovine detected lesions among Histology Positive lesions

The definition of Specificity within this framework is:

Sp(Test) = Proportion of histology Negative lesions that were not detected by Fluciclovine

Note here that this definition differs significantly from a more standard definition:

Sp(Test) = Proportion of histology Negative lesions that were Fluciclovine detections.

That is, for this Study, all Test detections default to Diagnostic Positives in the statistics.

Region Level: The SOT defaults to regions with at least one lesion detected and validated by histology as Positive or Negative. Given this SOT population, Fluciclovine Sensitivity at Region Level is:

Se(Test) = Proportion of Fluciclovine Positive Regions among all Positive Regions, where:

- (a): A Region is Positive if at least one detected and histology Positive lesion is in the Region
- (b): Fluciclovine is Positive for the Region if at least one Fluciclovine detection in the Region has Positive histology.

What about Region-Level Specificity? The requirement for inclusion of a Region is that it have histology validation for at least one lesion detected within it. Then the Region is Negative if all lesions detected and histology validated within the Region are Negative, and *Fluciclovine matches the Region for Negativity only if it makes no detections there*. So:

Sp(Test) = Proportion of Negative Regions without Fluciclovine detections where:

The region has histology validated lesions, all of them SOT Negative.

Subject Level: The Sot defaults to patients with histology validation (Positive or Negative) for at least one Region. This, in turn defaults to patients with at least one histology validated lesion. Then, a patient is Positive if at least one lesion has Positive histology. So:

Se(Test) = Proportion of Fluciclovine Positive patients among all Positive patients

Note that, using the logic presented under Region Level:

Sp(Test) = Proportion of patients without Fluciclovine detections among all patients for whom there were detections, all of which had Negative histology.

Primary Endpoint

The Sponsor's Primary Endpoint is Positive Predictive Value (PPV). This Endpoint can be defined at several levels – lesion/region/subject. Thus, for any level, call it Level L:

PPV = Proportion of SOT Positives at Level L among Fluciclovine detections at Level L

Thus, if the focus is Lesion Level:

PPV = Proportion of SOT Positive lesions among Fluciclovine Lesion Detections

Region PPV=Proportion of SOT Positive Regions among Fluciclovine Positive Regions

Subject PPV=Proportion of SOT Positive Subjects among Fluciclovine Positive Subjects

Primary Statistical Objective

The Primary Statistical Objective is to demonstrate that, for the Prostate/Bed Region:

(*): Success Criterion (*) $PPV > .50$ (Chance)

The Sponsor states that (Protocol April 2015, Synopsis p 12):

Eighty five patients with complete data will be required to demonstrate statistical significance for the effectiveness of PPV, based on using the *one-sided Exact Binomial Test* to compare $H_0: PPV \leq .50$ versus $H_1: PPV > .50$ with an assumed observed PPV of .65, a one-sided Type I error at .025, and with Power at least .80.

In this Review point estimates of PPV and other statistical performance measures will be provided at Lesion/Region/Subject levels, but Success Criterion(*) will be assessed only at the Prostate/Bed Level and at the Subject Level, since these are the levels with clinical meaning. Moreover, the achievement of Criterion(*) will be identified with:

Lower Limit of the One-Sided 97.5% CI of $PPV > .50$.

Some Preliminary Comments:

Comment#1: A Stand-Alone Criterion is seldom if ever an adequate gauge of Efficacy. For instance, (*) would be easily achieved ($PPV = 1.00\%$) if every image was read to have lesion detections everywhere. There needs to be some constraint that tempers (in this case) “overcalling”. In the current context, this could be Sensitivity, since this measure would Be reasonably high only if the detections were generally True Positives by Histology instead of being merely detections. Of course, an alternative set of measures could be Sensitivity and Specificity, but Specificity appears to be somewhat unnatural in this Study, so the Reviewer favors the following pair of Objectives:

(A): $PPV > PPV(0)$ ($PPV(0)$ some appropriate lower level of performance)

(B): $Sensitivity > Se(0)$ ($Se(0)$ some appropriate lower level of Performance)

The Sponsor set $PPV(0) = .50$, which the Reviewer considers low. It is not clear what $Se(0)$ should be, so Lower Limits of 97.5% One-Sided CIs for Sensitivity will simply be reported. In any event, adequate levels attached to (A) and (B) capture (with one caveat) the success scenario:

Fluciclovine detections have high probability of being detections of metastases, and metastatic detections (by any means) have high probability of having been Fluciclovine detections.

Caveat: *PPV is influenced by Disease Prevalence. (More on this later.)*

Comment#2: The Primary Analyses were based on On-Site Image reads, not on blinded reads. However, per FDA recommendation, a blinded read (three independent readers) of the Emory Test Images was conducted at the University of Bologna. The results from these reads will be presented alongside the On-Site results.

Comment#3: It is important to note that Sensitivity and Specificity, as defined in this Study, are not standard versions of these measures. In the standard scenario the Test Imaging Modality's performance is assessed with respect to an independent Standard of Truth (SOT) whose findings are not in any way directed by the Test. However, in the context of this Study, the Test Modality is a major contributor to whatever it is that the SOT evaluates (Verification Bias.) The general scenario that captures the current situation is the following:

The anatomical area under investigation is a collection of locations. In the standard scenario each location in the area is evaluated by the SOT. In the current scenario only those locations for which either a Test Modality or a Control Modality provide detections are evaluated by the SOT. Thus, the performance of the Test is really a relative performance of the Test with respect to the Truth status of locations that it and/or the Control provide for Truth evaluations. Thus, it is a theoretical possibility that, say, the anatomical area contains 10 distinct locations, but only 5 of these have Test and/or Control detections. It should, however, be understood that this scenario is not unusual, but, rather, has been the dominant scenario in most submissions over the last few years.

Additional Remark per this comment: The Control here includes all means through which location detections are made, such as other Imaging Modalities and random biopsies.

Comment#4: The expectation in the current Study is that most patients are recurrent for prostate cancer. However, the SOT provided is limited to evaluations of only those patients for whom lesions were detected by Test and/or Control. So Prevalence of disease in this Study means the proportion of patients for whom detected and excised lesions had positive histology. The patients who were not validated by histology could be validated as Positives through other criteria, such as continued rising PSA, but such validations are the responsibility of a Secondary SOT and will not be addressed in this Review.

Primary Efficacy Results

Relevant Demographics (99 Subjects who met Inclusion Criteria for BED-001)

Race:

White = 71 (72%) ; Black = 17 (18%) ; Missing = 10 Subjects (10%) Asian = 1

Age:

Mean+/-Sigma = 67 +/- 8 yrs

Age>=65Yrs = 62 Subjects (63%) ; Age <65 Yrs = 35 Subjects (36%); 2 Missing

Patient Disposition (99 Subjects who met Inclusion Criteria for BED-001)

There were 115 Subjects in the R01 Study

A total of 99 of these qualified as suggestive of Disease Recurrence

These 99 provided 105 data points (6 patients with repeat scans)

Table(3): Lesion Level Statistics

	On -Site	RDR1	RDR2	RDR3
N (Lesions)	371	371	371	371
TP	126	98	99	75
FP	82	58	49	35
TN	131	155	164	178
FN	32	60	59	83
SE	80%	62%	63%	47%
SP	62%	73%	77%	84%
PPV	61%	63%	67%	68%
NPV	80%	72%	74%	68%

Comments

The highlighted cells provide the entries the Reviewer considers relevant. Note first that the Prevalence here (lesion level) is $(TP + FN)/371 = .43$.

Note also, for the Statistic: **AV = (1/ 2)(Sensitivity + Specificity):**

AV: On-Site = 71% ; RDR1 = 73% ; RDR2 = 70% ; RDR3 = 66%

Table(4):Prostate/Bed (Parentheticals () contain Lower limits of 97.5% One-Sider CIs)

	On -Site	RDR1	RDR2	RDR3
N (Regions)	97	98	97	96
TP	57	58	56	47
FP	27	29	26	15
TN	12	10	12	24
FN	1	1	3	10
SE	98% (94%)	98% (95%)	95% (91%)	83% (73%)
SP	31% (16%)	26% (12%)	32% (17%)	62% (51%)
PPV	68% (58%)	67% (57%)	68% (58%)	76% (65%)
NPV	92% (77%)	91% (73%)	80% (60%)	71% (55%)

Comments:

For the On-Site reader and two of the three blinded readers the Sensitivity levels are close to 100%, so that, there is no concern that Fluciclovine fails to find metastases among those patients for whom metastases in the Prostate/Bed are established through some means of detection. However, the PPV is not especially good when looked at through lower limits of CIs, where it is generally not much more than slightly above chance levels (Chance = 50%.) Furthermore, Prevalence = (58/97) = 60%, and this figure impacts PPV. (The influence of Prevalence will be examined after presentation of the remaining tables.)

As for AV, as defined above:

AV: On-Site = 65% ; RDR1 = 62% ; RDR2 = 64% ; RDR3 = 73%

Note that Specificity levels are very low at the Prostate/Bed levels. For instance, for the On-Site Reader, we have a False Positive Rate of about 70%. Effectively, for 7 out of 10 patients for whom no lesion detections by any means were SOT Positive, Fluciclovine detected at least one such lesion.

Table(5): Extra-Prostatic

	On -Site	RDR1	RDR2	RDR3
N (Subjects)	29	28	28	25
TP	27	25	26	22
FP	2	2	2	2
TN	0	0	0	0
FN	0	1	0	1
SE	27/27 (100%)	25/26 (96%)	26/26 (100%)	22/23 (96%)
SP	0/2	0/2	0/2	0/2
PPV	27/29 (93%)	25/27 (93%)	26/28 (93%)	22/24 (92%)
NPV	0/0	0/1	0/2	0/1

Comments

In this region, but subject to the small numbers of patients involved, Fluciclovine revealed considerable Efficacy. The Reviewer's inference is that no means of detection other than Fluciclovine was operating here; a larger sample, with results consistent with these results, would strongly suggest that Fluciclovine is highly efficacious in locating metastases outside the Prostate/Bed.

Table(6): Subject Level (Parentheticals () contain Lower limits of 97.5% One-Sider CIs)

	On -Site	RDR1	RDR2	RDR3
N (Subjects)	105	103	104	98
TP	73	74	71	62
FP	19	24	23	13
TN	12	5	7	15
FN	1	0	3	8
SE	99% (97%)	100%	96% (91%)	89% (83%)
SP	39% (19%)	17% (3%)	23% (8%)	54% (35%)
PPV	79% (71%)	76% (67%)	76% (67%)	83% (74%)
NPV	92% (77%)	100%	70% (40%)	65% (45%)

Comments

The Reviewer believes the Subject-Level results are the most important.

Note: Prevalence = 74/105 = 70%.

AV: On-Site = 67% ; RDR1 = 59% ; RDR2 = 60% ; RDR3 = 72%

On-Site:

PPV = 79% (Lower Limit of CI = 71%) ; Sensitivity = 99% (Lower Limit of CI = 97%).

Thus:

(1): 8 out of 10 patients for whom Fluciclovine finds lesions are metastatic by the SOT

(2): Virtually all metastatic patients had Fluciclovine detections that were SOT Positive

These results are strong evidence for Fluciclovine Efficacy, subject to one caveat:

The 70% Prevalence could be driving PPV. If, for instance, Prevalence were 50%, and if Sensitivity and Specificity stayed at the levels provided in the Table, then:

PPV drops from 79% to 63% , with Lower Limit of CI = 52%.

Conclusions

The Reviewer has focused on Subject Level statistics as the critical level relevant to Efficacy since it is this level that is most important clinically. The Reviewer has also focused on two measures as relevant to Efficacy, namely PPV and Sensitivity, for the following reasons:

(1): PPV is the Sponsor's Primary Endpoint

(2): Some measure that acts as a corrective to the Stand-Alone of PPV is necessary, and Sensitivity is meaningful here.

The results for BED-001 for these two measures are:

On-Site:

PPV = 79% (Lower Limit of CI = 71%) ; Sensitivity = 99% (Lower Limit of CI = 97%).

Thus, at least 7 of 10 patients with Fluciclovine detections will be metastatic for prostate cancer, and virtually all patients metastatic for prostate cancer will have had Fluciclovine detections validated as Positive by the SOT of histology.

The caveats that attach to these positive results are:

(A): *Only patients with lesion detections (by any means) qualify for inclusion in the statistics. However, on the Subject level, all patients had lesion detection by some means (88% by Fluciclovine).*

(B): *Sensitivity is not standard Sensitivity; instead it takes the form:*

Sensitivity = Proportion among patients with SOT Positive lesions who were SOT Positive for Fluciclovine

(C): *PPV is driven somewhat by Prevalence.*

If these caveats are not troublesome from a clinical perspective, then the Reviewer concludes that Fluciclovine has been demonstrated to have Efficacy in this Study.

3.3 Evaluation of Safety

There were no significant Safety issues.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender/Race/Age

Table(5): Subset Statistics (Race & Age Group)

	RACE		AGE	
	White (71 Subjects)	Black (17 Subjects)	≥ 65 (62 Subjects)	< 65 (35 Subjects)
Sensitivity	96%	92%	96%	91%
Specificity	38%	60%	31%	54%
PPV	79%	85%	80%	78%
NPV	89% (8/9)	75% (3/4)	71% (5/7)	88% (7/8)

Comments:

Specificity is higher for the Black population versus the White population, but there were only 17 Black patients (18%), so no conclusions will be drawn.

Specificity is significantly higher for the < 65 yrs population versus the ≥ 65 yrs population. The reviewer has no verifiable explanation for this.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This NDA is primarily a retrospective evaluation of patients who have had therapy for primary prostate cancer and have met an inclusion criterion of rising PSA, which is strongly suggestive of cancer recurrence. The investigation of recurrence, which is the primary objective of the investigation, consists of histological evaluation of lesions detected through Test Images, Control Images, or other techniques. Since patient management is largely dependent on whether recurrence is limited to the Prostate/Bed or is additionally or exclusively outside this area (Extra-Prostatic), the lesion detections are assigned a location, (Prostate/Bed; Extra-Prostatic), and Test Efficacy then consists in achieving reasonably high levels of correct diagnoses in these two regions, and also at the patient level.

The principal retrospective analyses conducted by the Sponsor were dedicated to the evaluation of Diagnostic Performance measures, such as Positive Predictive Value (PPV), Sensitivity, etc. The Sponsor's primary study is titled BED-001, and was based exclusively on data, and largely on the previous analyses, provided by an Emory Study (Study R01), whose principal results were published in Schuster et al, Journal of Urology, 2014. This review will concentrate almost exclusively on the Sponsor's Emory Study BED-001, the exception being the addition of

analyses of blinded read results of the Emory data conducted, under Sponsor direction, at the University of Bologna.

A large number of detected lesions (371), gathered from these several Imaging sources, along with other biopsied lesions not directed by images, underwent histology evaluation. In broad terms, the Study Objective was to establish that the Test Modality, on its own, provided Efficacy with respect to Subject and Region classifications for disease recurrence.

The Sponsor's Primary Endpoint is Positive Predictive Value (PPV). This Endpoint can be defined at several levels – lesion/region/subject. Thus, for any level, call it Level L:

PPV = Proportion of SOT Positives at Level L among Fluciclovine detections at Level L

The Primary Statistical Objective is to demonstrate that, for the Prostate/Bed Region:

(*): Success Criterion (*) PPV > .50 (Chance)

The original Emory On-Site read and the blinded reads were evaluated for various Performance Characteristics. The Sponsor's single Primary Statistic, PPV, achieved values > 50%. Since PPV as a Stand-Alone addresses the levels at which the Test correctly predicts metastases, but not how often it misses metastases, Sensitivity was included by the Reviewer as a significant endpoint. Sensitivity (SE) was typically very high at both Subject and Region levels.

Overall Conclusions

The Reviewer concludes that Fluciclovine Efficacy has been established.

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/s/

ANTHONY G MUCCI
02/19/2016

THOMAS E GWISE
02/19/2016

I concur with the reviewer. The product showed adequate diagnostic performance with respect to sensitivity and specificity.

JYOTI ZALKIKAR
02/19/2016

I generally concur with the primary reviewer.