

**CENTER FOR DRUG EVALUATION AND
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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 203-155

Supplement #:

Drug Name: Choline C 11 Injection , 370 to 740 MBq (10 to 20 mCi) administered as a bolus intravenous injection

Indication(s): Diagnostic PET (positron emission tomography) imaging for identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

Applicant: Mayo Clinic PET Radiochemistry Facility

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1 EXECUTIVE SUMMARY

The Mayo Clinic is seeking approval for Choline C 11 Injection PET to be used for the identification of (b) (4) recurrence of prostate cancer in patients following primary (b) (4)

This submission comprised of a total of 12 studies. Five studies are prospective studies from literature review (3 studies for C11 and 2 studies for F18). Seven studies are retrospective studies (6 studies are from literature and one study conducted by Mayo clinic).

Key studies identified are 3 prospective studies for C11 (Breeuwsma et al. 2010, Richter et al. 2010, Garcia et al. 2009) from literature review and the retrospective study conducted by Mayo clinic (Mayo study).

Among the 3 prospective studies for C11, Garcia et al. 2009 included only 38 patients (sample size is too small), the results presented by Richter et al. 2010 (73 patients) are not clear (more details in the main body of the review). Only Breeuwsma et al. 2010 had relatively large sample size (70 patients) and clear results. The Mayo study data is inspected but the study results are not published.

The **detection rate** of C11 PET (positive C11 PET among all enrolled patients) and the 95% exact confidence intervals in percent are 81 (70, 90) from Breeuwsma et al. 2010, 61 (48, 72) from Richter et al. 2010, 68 (51, 82) from Garcia et al. 2009, and 75 (68, 81) from the Mayo clinic retrospective study. The detection rates increase with increasing PSA levels.

Breeuwsma et al. 2010 showed 41/57 patients with positive scan have local recurrence identified of which 26/41 cases were confirmed by biopsy, 15/41 cases by clinical course and PSA response to local salvage treatment. This paper also showed that 16/57 cases had locoregional and or distant recurrence (8 proven by additional CT or MRI, 1 by histological evidence, 6 bone scanning, 1 false positive). **Richter et al. 2010** showed 23/43 cases with local recurrence by PET (15 in whole prostate area, 2 in right side, and six in the left) without clear confirmation information. **Garcia et al. 2009** showed 14/26 patients detected by C11 present focal uptake of C11, 8 of 14 were confirmed by biopsy, 4 of 14 were confirmed by a reduction in PSA following further radiotherapy and definitive diagnosis was not reached in 2 of 14 cases.

Mayo clinic retrospective study showed that 34 patients with negative conventional imaging underwent ¹¹C-choline PET/CT and subsequently had biopsies of suspected recurrence sites. The median PSA level of the 34 patients was 3.85 ng/mL (range 0.21 to 65.0 ng/mL); 22 of the patients had previously undergone radical prostatectomy and 12 (7 with radiotherapy) had received other therapy (radiotherapy, anti-androgen therapy or cryotherapy). ¹¹C-choline PET/CT images were positive in 30 patients and negative in four patients. Cancer was verified by histopathology in 29 patients; 25 had positive PET/CT images and 4 had negative PET/CT images. Five patients with positive PET/CT images did not have cancer confirmed with

histopathology. In the Mayo study, the median PSA was 4.2 ng/mL (range 0.24 – 65.0 ng/mL) among the 25 patients with true positive images; PSA levels < 2 ng/mL were observed in four of the nine patients with false negative or positive images.

In summary, the applicant's claim about C11 PET is supported by the combined information from the literature research and the study from Mayo clinic. However, there are caveats as noted in the following: 1) The quality of the data from the Mayo clinic is weak (see Section 3.1) especially due to the retrospective study design. 2) The patient-level data of the prospective studies from the literature are not available and so the results of these studies are not inspected.

Therefore, C11 PET should be used only when other conventional imaging approaches fail to identify local or distant disease in patients with recurrent prostate cancer.

2 INTRODUCTION

2.1 Overview

2.1.1. Indication

The sponsor seeks approval for the following indication:

“Identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

Patients who exhibit “**primary treatment failure**” are defined as men with prostate cancer who have previously been treated with at least one form of therapy including, but not limited to, radiation therapy, radical surgery, minimally-invasive prostate surgery (ie, cryotherapy, high intensity focused ultrasound [HIFU], proton-beam therapy) or systemic therapy (ie, hormonal therapy, chemotherapy). For further clarification, the phrase “**patients who have failed one or more conventional imaging modalities**” is intended to address men who previously failed primary therapy and in whom conventional imaging (ie, bone scan, computed tomography [CT] scan, or magnetic resonance imaging [MRI]) failed to reveal proper “next steps” in therapy.

2.1.2. History of Program Development

In many of the prostate cancer patients with treatment failure, Choline C 11 Injection evaluation has identified a solitary (isolated, focal) site of prostate cancer recurrence that was easily and effectively destroyed by a targeted approach instead of palliative systemic therapy. Mayo Clinic PET Radiochemistry Facility (Mayo clinic) has been able to spare many patients from experiencing unwarranted radiation-based or systemic therapy, and for select patients, the clinic has been able to redirect therapy from a palliative approach to an approach that is more likely to yield curative outcomes.

In order to support this NDA application, Mayo clinic conducted a retrospective study (Mayo Clinic study) examining the performance of Choline C 11 PET for evaluation of men for whom prior therapy for prostate cancer failed. In this study, the performance of Choline C 11 was studied for its ability to delineate prostate cancer relapse after definitive therapy failed. The following primary endpoints were analyzed for this study: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and clinical usefulness.

In addition to the Mayo Clinic study, supportive efficacy information for this NDA document was drawn from literature searches. Published papers from 1950 to 2011, relevant to Choline C 11 for the indication being sought, were selected and reviewed using 3 major biomedical and scientific databases; PUBMED, National Library of Medicine, and MEDLINE through the ENDNOTE database search program. Using criteria pertinent to the indication, 11 articles focused on restaging prostate cancer after initial therapy in patients with suspected recurrence due to persistent or elevated PSA blood testing.

2.1.3. Specific Studies Reviewed

This submission comprised of a total of 12 studies. Five studies are prospective studies from literature review (3 studies for C11 and 2 studies for F18). Seven studies are retrospective studies (6 studies are from literature review and one study was conducted by Mayo clinic).

Key studies identified for review are 3 prospective studies for C11 (Breeuwsma et al. 2010, Richter et al. 2010, Garcia et al. 2009) from literature review and the retrospective study conducted by Mayo clinic (Mayo study).

A summary of the 4 studies is shown in Table 1.

Table 1: Summary of the key studies in the review

Study title	Sponsor or authors (year)	Design	Sample size	Agent studied
PET/CT with 11C-choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer.	García JR, M. Soler M, Blanch MA, Ramírez I, Riera E, Lozano P, et al. (2009)	Prospective Single arm, partial subject level data available in the article	38 all patients with recurrence (positive)	C11 and FDG
Detection of local, regional, and distant recurrence in patients with PSA relapse after externalbeam radiotherapy using 11C-choline positron emission tomography.	Breeuwsma AJ, Pruim J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, et al. (2010)	Prospective, single arm, no subject level data	80 (70 positive+10 negative control)	C11
Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment.	Richter JA, Rodríguez M, Rioja J, Peuelas I, Mart-Climent J, Garrastachu P, et al. (2010)	Prospective, single arm, no subject level data	73 all patients with recurrence (positive)	C11 and FDG
Choline C 11 positron emission tomography (PET) scan for patients with prostate cancer, with biochemical recurrence following failed initial treatment	Mayo clinic 2010	Phase N/A, Retrospective, patient chart review; no formal prospective research protocol was performed, subject level data available by Mayo clinic	176 all patients with recurrence (positive)	C11

In the following, only the retrospective study conducted by Mayo clinic (with subject level data available) is reviewed in detail. The results of the three prospective studies from published articles are summarized according to the results presented by the authors in the article. Some results were verified using the partial data provided in those articles by FDA statistical reviewer.

2.2 Data Sources

All materials reviewed including the applicant study reports, data sets and literature referenced are provided electronically, and the full electronic path of the documents are <\\Cdsesub1\evsprod\NDA203155\0000> and <\\Cdsesub1\evsprod\NDA203155\0001>

The application study reports include Clinical overview, Summary of Clinical Efficacy, Summary of Clinical Safety in <\\Cdsesub1\evsprod\NDA202008\0000>, M2.

The data sets for the Mayo retrospective study are in <\\Cdsesub1\evsprod\NDA203155\0001> M5. The datasets analyzed include [petchdat1.xpt](#) and [petchdat2.xpt](#).

The sponsor did not provide data for the studies from literature review.

3 STATISTICAL EVALUATION

Only the Mayo clinic retrospective study is explored in detail in this section. For the 3 prospective studies selected from literature review, we only describe their design and report their results in Section 3.2.5. We do not conduct analyses and inspect the data sets in the three prospective studies.

3.1 Data and Analysis Quality

Only the quality of the Mayo clinic study is evaluated below.

Data quality:

In the original submission, the sponsor provided a data set including baseline variables, test results from PET (Positive and Negative), true standard decided by the definition described in section 3.2.3.

The study had neither protocol nor analytical plan. A data collection format (a table) was developed to contain information extracted from medical records. The study was exempted from IRB review and patients did not provide consent. The study report findings may not be traceable back to original source data.

In the original submission, there is no information on biopsy, surgical resection, conventional image, location of recurrence identified by PET in the 1st data set.

The sponsor provided the 2nd data set after FDA's information request. However, some information is not clear in this data set and some variables are not correct:

- It is not clear if the location of 1st recurrence, location of 2nd recurrence, and the location of 3rd recurrence are determined by the C11 PET or the other approaches (biopsy, resection, conventional imaging). In this review, we assume that the locations of recurrences reported in variables loc1rec, loc2rec and loc3rec are determined by some means (PET scan, or conventional imaging approaches, or biopsy, or surgical resection). Some of them are confirmed by biopsy and surgical resection to be positive, some of them are confirmed by biopsy and resection to be negative and some of them are not confirmed by biopsy or resection at all.
- Con_imag in the data had values 0 (negative) and 1 (positive). We can also generate con_imag2 using variables ctscan, bonscan (bone scan), mri and prosscscan (proscint scan) (all having values 0 for negative, 1 for positive, and missing) according to the following algorithm:

```
Sum con=sum(ctscan, bonscan, mri, prosscscan);  
if sum con>=1 then con_imag2=1;  
if sum con=0 then con_imag2=0;  
if sum_con=. then con_imag2=.;
```

The values of the generated conventional imaging variable `con_imag2` are not consistent with the values of `con_imag` provided in the data set by the sponsor. There are 75 zeros, 96 ones, and 5 missing values in `con_imag`. There are 79 zeros, 94 ones, and 3 missing values in `con_imag2`.

- The “Disease” variable in the data had value 0 (not confirmed), 1 (confirmed disease) and missing values. According to the sponsor’s definition, disease can be confirmed by biopsy, surgical resection, conventional imaging, and more than 50% reduction in PSA after selective radiation to Choline avid lesions (four elements). We generate “Disease” variable using the four elements in the data provided by the sponsor, the values for the generated variable are not consistent with the values provided by the sponsor.
- Consider the variability in PSA testing, conventional imaging, biopsy and surgical resection, the Standard of Truth (SoT) to confirm the “disease” is weak.

The two variables (`con_imag` and Disease) generated by FDA reviewer using the sponsor’s definition will be used in the later analyses instead of the two variables provided by the sponsor.

Analysis quality:

The study is a retrospective study. Sponsor analyzed the 1st data set only and obtained the so called “sensitivity”, “specificity”, “PPV” and “NPV” using the 1st data set. Using the same data, we can obtain the same numbers with additional 95% exact confidence interval. However, because the Standard of Truth used by the sponsor is not a real Standard of Truth, the four measures are not clinical meaningful.

The definition of sensitivity is not the same in the sponsor analyses and the selected articles. Basically, from the selected articles, the “sensitivity” values are detection rate of positive disease by C11 PET among all patients with disease (participated in the studies), but not the matching rate of C11 PET and the other approaches including biopsy, resection, and conventional images (used by the sponsor). Therefore, we notice higher sensitivity (93%) value from Mayo clinic study than the values from the other studies in literature.

In the following analyses, we will not report the sensitivity and specificity defined by Mayo clinic. Instead, we will report the detection rate (sensitivity defined by the selected articles) of positive C11 PET results among all 176 patients enrolled in the retrospective study.

3.2 Evaluation of Efficacy

The Efficacy evaluation for Mayo study is described in Sections 3.2.1 to 3.2.4. The Efficacy from the literature articles is summarized in Section 3.2.5.

3.2.1 Study Design and Endpoints

- Objective: evaluate the use of **C11 Choline** PET for the identification of local, lymph node, and distant recurrence of prostate cancer in patients after primary treatment failure

and in patients who have failed one or more conventional imaging modalities for localization of recurrent prostate cancer.

- Sample size: 176 patients (among 231 patients who underwent the PET imaging between September 2007 and November 2010)---all failed primary therapy defined by BCR (i.e., a rising PSA determined by at least 2 separate PSA measurements acquired 3 months apart for patients initially treated with radical prostatectomy, or nadir plus 2 ng/mL for patients treated with radiation or primary cryoablation, or a steady rise in PSA for men treated with primary androgen deprivation therapy (ADT))
- Reader: images read only by experienced staff nuclear medicine physicians. No set of routine was followed with regards to order, type, or timing of imaging obtained.
- Confirmation:
 - A PET scan was considered a “true positive” if any of the following was shown:
 - Histologic confirmation by targeted biopsy or surgical resection
 - Confirmation by conventional imaging,
 - or decrease in PSA >50% after selective irradiation of Choline-avid lesions.
 - A PET scan was considered a “true negative” if either of the following was shown:
 - Disease was absent on the biopsy results or surgical resection
 - Confirmation with negative conventional imaging.
- Subject level data available
- Measurements included sensitivity, specificity, PPV, NPV and clinical usefulness.

3.2.2 Statistical Methodologies

A PET scan was considered a “true positive” if any of the following was shown:

- histologic confirmation by targeted biopsy or surgical resection, or
- confirmation by conventional imaging, or
- a decrease in PSA >50% after selective irradiation of Choline-avid lesions.

A PET scan was considered a “true negative” if either of the following was shown:

- disease was absent on the biopsy results or surgical resection, or
- confirmation with negative conventional imaging.

The following primary endpoints were assessed: sensitivity, specificity, PPV, NPV and clinical usefulness. *The first four measures evaluates the 2 by 2 table of Test results (by PET) versus True disease (True negative and True positive defined above). The Standard of Truth is questionable according to medical team and all patients with recurrent prostate cancer should be used for sensitivity analyses and any patients without recurrent prostate cancer (any controls or true negative cases) should be used for specificity analyses. Statistically, the variability in PSA testing, conventional imaging, biopsy and surgical resection can not provide a reliable*

Standard of Truth (SoT) to confirm the “disease”. This may lead to biased estimation for sensitivity and specificity. In this study, we only see patients without any controls (true negative cases) enrolled. Therefore, we can not evaluate sensitivity and specificity, but we do evaluate detection rate defined as proportion of positive scans among all patients.

There is no definition of clinical usefulness described in the submission. We do not evaluate it in this review.

For both categorical and continuous measures, demographic, clinical, and pathology data were summarized by 2 groups, patients for whose PET/CT scan was negative (failed to locate any evidence of recurrent prostate cancer) or patients whose PET/CT scan was positive (i.e., recurrence of prostate cancer or distant metastasis).

Only the summaries for all patients are presented in section 3.2.2. The definitions of the true positive and true negative are questionable (see earlier comments).

Multivariate modeling was conducted of positive Choline C 11 PET scan result and confirmed disease. Additionally, multivariate modeling of positive Choline C 11 PET scan result at the time of the test (all treatment options) was conducted.

According to the sponsor, any record with any missing values will be removed in the modeling. Some variables have many missing values. For example, about half of the clinical staging values are missing. The records used in the multivariate modeling are only half of the total records, which lead to selection bias. Therefore, in this review, only single variables are included in the logistic modeling for positive PET results and confirmed disease.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Available patient’s baseline characteristics are presented in Tables 2 and 3. There is no information on race and gender in the data sets. All 176 patients are included in the study.

The mean (and median) Age at diagnosis of prostate cancer is 60 with minimum value as 42 and maximum value as 78. Age at treatment (mean and median as 61) is a little bigger than age of diagnosis. The mean (and median) age at PET is 71, which is about 10 years after age at diagnosis. The distributions of ages are symmetric. The mean year from cancer diagnosis to the PET imaging is 10 years with range from 3 years to 29 years.

The distribution of PSA variables are not symmetric (right skewed). The median PSA level at PET for the 176 patients is 3.2 with range from 0 to 189. The median time from initial treatment to biochemical failure is 24 months with range from 0 to 204 months.

Most of the patients had Prostatectomy treatment after diagnosis of prostate cancer. Very few patients received Cyosurgery (3 subjects) and Androgen Deprivation Therapy (5 subjects).

More patients had Gleason score 7 (89 subjects) than other ones with score 6 and 7. More than half patients had missing clinical staging values. Most patients had 0 nodes (110 subjects).

There are 59 subjects with missing pathological T-staging. And there is no subject with T0 among the subjects with available pathological T-staging (only T2 and T3).

Fifty four patients received Androgen deprivation therapy at the time of PET scan. Only 85 patients (not include the ones with missing values) received additional treatment (adjuvant or salvage). And most of the 85 patients received Radiotherapy (62 subjects) as the additional treatment.

Table 2: Summary of baseline variables (continuous)

	N missing	Mean	std	median	Min	Max
Age at treatment	0	61	7	61	42	78
Age at diagnosis	0	60	7	60	42	78
Age at pet scan	0	71	8	71	49	90
Y from diagnosis to Pet	0	10	5	9	3	29
PSA at diagnosis	34	30.8	113.2	7.2	2.2	1028
PSA at pet scan	0	9.7	23	3.2	0	189
PSA doubling time	23	8.8	15.5	5.7	0.4	179
PSA velocity	23	1.1	2.9	0.3	0.01	21.7
Initial treatment to biochemical fail in months	31	38	41	24	0	204

Table 3: Summary of baseline variables (categorical)

Variable		Frequency	Percent (freq/176)
Treatment	0 (RRP: Prostatectomy)	126	71.6
	1 (XRT: Radiotherapy)	41	23.3
	2 (Cryo: Cryosurgery)	3	1.7
	3 (ADT: Androgen Deprivation Therapy)	5	2.8
	Missing	1	0.6
Clinical gleason score	6	27	15.3
	7	89	50.6
	8	52	29.5
	Missing	8	4.5
Clinical staging	0 (T1c)	41	23.3
	1 (T2, 2a, 2b, 2c)	39	22.2
	2 (T3, 3b)	12	6.8
	Missing	84	47.7
Nodes	0	110	62.5
	1	11	6.3
	Missing	55	31.3

Pathological T-stage	T2a	1	0.6
	T2b	24	13.6
	T2c	32	18.2
	T3a	30	17
	T3b	30	17
	Missing	59	33.5
ADT (Androgen deprivation therapy) at PET scan	No	119	67.6
	Yes	54	30.7
	Missing	3	1.7
Additional treatment	No therapy	47	26.7
	Adjuvant	51	29
	Salvage	34	19.3
	Missing	44	25
Type of additional treatment	ADT: Androgen Deprivation Therapy	21	11.9
	XRT: Radiotherapy	62	35.2
	Chemo: Chemotherapy	1	0.6
	Missing	92	52.3

In the data from Mayo study, only one subject has decrease in PSA >50% after selective irradiation.

3.2.4 Results and Conclusions

Brief summary of the applicant's results and conclusion

Mayo clinic believes that Choline C 11 PET evaluation not only facilitates proper treatment assignment by differentiating between viable versus non-viable sites of prostate cancer recurrence, but also does so at an earlier point during disease relapse. It is also for this reason that they believe that Choline C 11 PET provides substantive advantages over conventional imaging for the management of patients for whom primary prostate cancer therapy failed.

From the Mayo retrospective study, the following results are summarized:

- Evaluation using Choline C 11 PET is particularly useful for identifying sites of prostate cancer recurrence in men for whom one or more prior therapies for treatment of prostate cancer failed.
- Choline C 11 (PET) scan was able to delineate the distribution and extent of prostate cancer relapse in 176 patients after failure of initial therapy.

- Abnormal lesions exhibiting increased uptake of Choline C 11 were interpreted as “choline-avid” tissues consistent with sites of prostate cancer metastasis or relapse (collectively termed recurrence)
- Detection of recurrence using the Choline C 11 PET scan was shown to have a sensitivity of 93% and a specificity of 76%, when compared with “gold standard” biopsy plus imaging for patients receiving all forms of available prostate cancer treatment
- Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 91% and 81%, respectively, for this population of patients. Choline C 11 PET scan appeared to perform even better when considering only the subset of patients treated by Prostatectomy compared to the more heterogeneous all-patient population, with a sensitivity, specificity, PPV, and NPV of 95%, 86%, 94%, and 89%, respectively.

Published studies outside of Mayo support our observation of enhanced early-lesion detection using Choline C 11 PET. The collective literature, combined with the Mayo experience, clearly supports the advantage of using Choline C 11 PET, over conventional imaging, for identifying sites of prostate cancer relapse in men for whom prior prostate cancer therapy failed.

The above results are all from the sponsor. In the following, we provide results from FDA.

FDA Results from the Mayo clinic study

The sensitivity, specificity, PPV and NPV values provided by Mayo clinic in the above paragraphs are not proper with a good Standard of Truth. Therefore, we do not evaluate them in this review.

The results for the Mayo clinic study from FDA is provided below.

Detection rate:

We report detection rate (positive PET scan / total number of patients) instead of sensitivity, specificity, PPV, and NPV because there is no well defined Standard of Truth for evaluating the PET test results.

The detection rate of C11 PET is 75% with 95% confidence interval (68%, 81%).

Table 4: Mayo study Frequency of positive C11 PET scans and % (detection rate)

Group (total n)	Freq of pos scans	% and 95% CI
All (176)	132	75 (68, 81)

Logistic regression modeling:

For model using PET as response, if PET result is positive, we let response as 1, otherwise, as 0. For model using disease as response, if disease is positive, we let response as 1, otherwise, as 0. We include several variables in the model for evaluating the effect of the particular variables. Only one variable is included in each model. All baseline variables described in section 3.2.2 were evaluated. Only model with significant variables are presented.

The Odds ratio (CIs) and pvalues are shown in Table 5.

It turns out the older the patients with higher PSA at the time of PET, higher the risk of getting positive PET results and positive disease.

If treating clinical staging (0, 1, 2), and gleason score (6, 7, 8) as numeric values, patients with higher clinical stage, or higher gleason scores tends to have higher risk of getting positive disease.

Table 5: Effect of variables on positive PET results and positive disease

Single variable logistic model (only present significant variables)					
Size	response	Variable in the model	Odds ratio	95% CI	Pvalue
176	Positive PET	Age_pet	1.05	(1.006, 1.104)	0.0278
176	Positive PET	Log2PSA_pet	1.35	(1.133, 1.611)	0.0008
160	Positive disease	Age_pet	1.05	(0.998, 1.096)	0.0583
160	Positive disease	Log2psa_pet	1.264	(1.07, 1.493)	0.0058
85	Positive disease	Clinic stage (numeric)	6.28	(2.285,17.241)	0.0004
If the categorical clinical stage (0, 1, 2) is used, the model can not be fitted.					
153	Positive disease	Clinic gleason score (numeric)	1.83	(1.062, 3.161)	0.0296
If the categorical (6, 7, 8) gleason score is used, this variable is no longer significant in the model.					

Disposition of patients by conventional imaging, PET scan and confirmation by biopsy or surgical resection

The numbers of patients in each stratum are presented in the following table with PSA at PET scan. PSA level at PET scan is higher in the subjects with positive conventional imaging results

or positive PET results. For patients with negative conventional imaging results, and positive PET scan results, the confirmed positive cases have higher PSA levels at PET (median 3.8ng/mL) than those for the confirmed negative cases (median 4.2 ng/mL). For patients with positive conventional imaging results, and positive PET scan results, the confirmed positive and negative cases are similar (median as 3.8-3.9 ng/mL).

Thirty four (4+5+25) patients with negative conventional imaging underwent ¹¹C-choline PET/CT and subsequently had biopsies of suspected recurrence sites. The median PSA level of the 34 patients was 3.85 ng/mL (range 0.21 to 65.0 ng/mL); 22 of the patients had previously undergone radical prostatectomy and 12 (7 with radiotherapy) had received other therapy (radiotherapy, anti-androgen therapy or cryotherapy). ¹¹C-choline PET/CT images were positive in 30 patients and negative in four patients. Cancer was verified by histopathology (biopsy or surgical resection) in 29 patients (4+25); 25 had positive PET/CT images and 4 had negative PET/CT images. Five patients with positive PET/CT images did not have cancer as confirmed with histopathology. In the Mayo study, the median PSA was 4.2 ng/mL (range 0.24 – 65.0 ng/mL) among the 25 patients with true positive images; PSA levels < 2 ng/mL were observed in four of the nine patients with false negative or false positive PET images.

Thirty six (2+5+29) patients with positive conventional imaging underwent ¹¹C-choline PET/CT and subsequently had biopsies of suspected recurrence sites. The median PSA level of the 36 patients was 3.45 ng/mL (range 0 to 65 ng/mL); 22 of the patients had previously undergone radical prostatectomy and 14 had received radiotherapy. ¹¹C-choline PET/CT images were positive in 34 (5+29) patients and negative in two patients. Cancer was verified by histopathology in 31 (2+29) patients; 29 had positive PET/CT images and 2 had negative PET/CT images. Five patients with positive PET/CT images did not have cancer as confirmed with histopathology. In the Mayo study, the median PSA was 3.8 ng/mL (range 0 – 65 ng/mL) among the 29 patients with true positive images; PSA levels < 2 ng/mL were observed in 2 of the seven patients with false negative or false positive PET images.

The confirmed cancer recurrence could be local, lymph node, bone, or distant. Most of the confirmed cases are local and lymph node.

Note that the stratification in Table 6 is conducted according to the medical practice. Patients first go through conventional imaging for suspected recurrence of prostate cancer. If the results from conventional imaging are negative and the PSA level is high, they will be evaluated by PET. Finally, biopsy or surgical resection are used to confirm the disease if any positive results are detected by some imaging tools.

Table 6: Patients disposition in the Mayo data

PSA at PET scan is presented as [median, range(min, max)].

Approaches	Outcome					
Conventional imaging	Negative					
	79 [PSA: median 2.8, range (0, 65)]					
PET scan	Negative			Positive		
	35 [PSA: median 1.3 range (0, 13.1)]			44 [PSA: median 4.25 range (0.24, 65)]		
Confirmed by histopathology	negative	positive	Not confirmed	negative	positive	Not confirmed
	0	4 [0.77 (0.21, 8.6)]	31 [1.4 (0,13.1)]	5 [3.8(0.96,1 1.3)]	25 [4.2 (0.24, 65)]	14 [6.65 (1, 27)]
		3 local, 1 lymph node			8 local, 14 lymph node, 2 bone, 1 distant	
Conventional imaging	Positive					
	94 [PSA: median 3.75, range (0, 189)]					
PET scan	Negative			positive		
	8 [median 2.05, range (0, 102)]			86 [median 3.9, range (0, 189)]		
Confirmed by histopathology	negative	positive	Not confirmed	negative	positive	Not confirmed
	4 [2.6 (0, 71.6)]	2 [0.17, 2.2]	2 [1.9, 102]	5 [3.9 (0.52, 5.5)]	29 [3.8 (0, 65)]	52 [4.25 (0.22, 89)]
		1 local, 1 distant			13 local, 12 lymph node, 3 bone, 1 distant	
Conventional imaging	Missing: 3 subjects					
PET scan	Negative			positive		
	1			2		
Confirmed by histopathology	negative	positive	Not confirmed	negative	positive	Not confirmed
	0	0	1 [PSA:36]	1 [PSA:8.3]	0	1 [PSA:2.2]
				biopsy		

* There is no missing outcome from PET scan.

Exploratory analyses on conventional imaging

In the following table, 0 indicates negative, 1 indicates positive, and missing indicates there is no result from that approach. If anyone of the four conventional approaches indicated a positive result, the conventional imaging indicated as positive result. There are 94 patients with positive results from conventional imaging approaches, 32 with positive results from Biopsy, and 34 from surgical resection.

Table 7: Summary of conventional imaging approaches

Approaches	Results	Frequency	Percent (freq/176) in %
Conventional imaging (including CTscan, Bone scan, MRI, and prostacint scan)	0	79	44.9
	1	94	53.4
	missing	3	1.7
CT scan	0	68	38.6
	1	30	17
	Missing	78	44.3
Bone scan	0	106	60.2
	1	22	12.5
	Missing	48	27.3
MRI	0	55	31.2
	1	61	34.7
	Missing	60	34.1
Prostacint scan	0	3	1.7
	1	1	0.6
	Missing	172	97.7

Time from conventional imaging to PET (months)

Most patients have the time from conventional imaging to PET less than one month (42% for CT scan, 53% for Bone scan, 55% for MRI). There are only five subjects having the information for Prostacint scan.

Table 8: Summary of time between conventional imaging and PET scan

	Time	Frequency	Percent
CT scan	0	74	42
	1	20	11.4
	2	7	4
	Missing	75	42.6
Bone scan	0	93	52.8
	1	28	15.9
	2	10	5.7
	Missing	45	25.6
MRI	0	96	54.5
	1	17	9.7
	2	4	2.3
	Missing	59	33.5
Prostacint scan	0	1	0.6
	1	2	1.1
	2	2	1.1
	Missing	171	97.2

Note: 0= 1 month or less, 1= More than 1 month until 2 months or less, 2= More than 2 months until 3 months or less

3.2.5 Summary of the three prospective studies from literature review

Breeuwsma 2010, Richter 2010, and Garcia 2009 are all prospective studies with single arm, open label. Patients are all recurrent prostate cancer patients.

Breeuwsma 2010

- Objective: study the potential of **C11-choline PET** to identify site of recurrence in patients with Biochemical recurrence (indicated by rising PSA) after electron beam radiation therapy (EBRT).
- Sample size: 70 positive cases (with histologically proven prostate cancer treated with EBRT and showing biochemical recurrence) + 10 control (true negative) cases (without biochemical recurrence after EBRT)
- Mean age is 50, and there is no range provided.
- PSA is grouped as 0-4, 4-10, >10
- Reader: Two independent experienced PET physicians, blinded for the clinical data
- Confirmation: biopsy findings (malignant), confirmation on additional images (CT, transrectal ultrasound, bone scan, MRI of the prostate), follow-up data (i.e., response to salvage therapy, decrease in PSA).
- No subject level data available
- Measurements included sensitivity, specificity, PPV, and accuracy.

Richter 2010

- Objective: Evaluate consecutive administration of both **F18-FDG** and **C11-choline** in patients followed by PET in the detection of biochemical prostate cancer relapse.
- Sample size: 73 patients with persistent increases in serum PSA
- Age: 41-78
- PS is grouped as >1.5 or not.
- Reader: an experienced PET physician, who was blinded to the clinical data.
- Confirmation: imaging results were confirmed by positive biopsy, increase in PSA during follow-up or decrease in PSA after the therapy.
- No subject level data available
- Measurements included sensitivity and proliferative parameters (Gleason score).

The sensitivity, specificity, accuracy, and positive and negative predictive values were calculated. Differences in continuous variables between groups were evaluated using the Student's t test or the Mann–Whitney rank sum test. Patient groups were compared using the Chisquare test. The Fisher exact test was used for comparison of frequencies, and Spearman correlation coefficients were calculated to quantify biivariate correlations.

Only patients with recurrent prostate cancer were enrolled in this study, so we call “sensitivity” as detection rate.

Garcia 2009

- Objective: compare the diagnostic accuracy of PET/CT with **F18-FDG** and **C11-choline** for early detection and localization of recurrent prostate cancer.
- Sample size: 38 consecutive patients that presented biochemical suspicion of recurrent prostate cancer
- Age: 56-71
- PSA is grouped as <1.0, 1-4, and >4
- Reader: images were read jointly by a specialist in nuclear medicine, and a specialist in radiodiagnosis who was unaware of the patients' clinical condition.
- Confirmation: biopsy, PSA decrease following therapy, other imaging techniques.
- Partial subject level data available (patient id, C11 results, PSA, FDG results, treatment)
- Measurements included abnormal deposits of tracer, detection of recurrence and the value of PSA.

FDA summary of the study results from literature review

The results are provided by the articles and we also verified some of the values using the available data information. The confidence intervals were calculated by FDA reviewer.

Breeuwsma 2010:

Table 9: Results from Breeuwsma 2010

	Sen	Spe	ppv	npv	accuracy
Breeuwsma et al. 2010 (C11)	57/70=81% (70%, 90%)	10/10=100% (69%, 100%)	57/57=100% (94%, 100%)	10/23=44% (23%, 66%)	67/80=84% (74%, 91%)

In addition to the above measures, we have the following:

41/57 patients with positive scan have local recurrence identified, 26/41 are confirmed by biopsy, 15/41 by clinical course and PSA response to local salvage treatment.

16/57 has locoregional and or distant recurrence (proven by additional CT or MRIC, bone scanning, histological evidence in 3 patients).

13/70 false negative of which 5 had biopsies: 3/5 with biopsies proven local recurrence, 1/5 negative carcinoma, 1/5 histological changes due to radiation therapy.

PSA 0-4: sensitivity 80%, PSA 4-10: sensitivity 73%, PSA >10: sensitivity 87%.

Richter 2009:

Table 10: Results from Richter 2009

		Detection rate
Richter et al. 2009 (C11 and FDG)	71 positive cases	C11: 43/71=60.6%, FDG: 22/71=31%, jointly: 44/71=62%

The total sample size is 73. According to the authors, there are two cases as true negative cases. Therefore, only 71 (73-2) positive cases were evaluated in the above table for detection rate calculation.

In addition, sensitivity for C11 is 80% and for FDG is 40% when excluding patients with PSA<=1.99.

Among 43 true positive by C11, 23 local recurrences were detected by C11 PET. However, the confirmation information is not clear in the article.

Garcia 2008

Table 11: Results from Garcia 2008

		Detection rate
Garcia et al 2008 (C11 and FDG)	38 positive cases	C11: 26/38=68% (n=26), FDG: 34%. PSA<1: C11 40%, FDG 0%; PSA1-4: C11 50%, FDG 13%; PSA >4: C11 87%, FDG 63%

In addition, 14 out of the 26 patients detected by C11 showed focal uptake of C11. Confirmed cases are 8 of 14 by biopsy and 4 by a reduction in PSA following further radiotherapy. Definitive diagnosis not reached in 2 of 14 cases.

3.3 Evaluation of Safety

There is no major safety issue for this product (For more details please see clinical review).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In Mayo study, frequency of positive C11 PET scans and % (detection rate) are shown by treatment, age group, time to initial treatment to biochemical failure and PSA at PET.

Patients with Radiotherapy, with age >65, time from initial treatment to biochemical failure more than 36 months, higher PSA values, have higher detection rate than those in the other groups.

Table 12: Detection rate and 95% Confidence intervals by subgroups

Group (total n)	Freq of pos scans	Detection rate in % and 95% CI
RRP (Prostatectomy) subjs (126)	91	72 (64, 80)
XRT (Radiotherapy) subjs (41)	35	85 (71, 94)
Age≤65 (39)	26	67 (50, 81)
Age>65 (137)	106	77 (69, 84)
Initial treatment to biochemical failure ≤36 month (122)	90	74 (65, 81)
>36 (54)	42	78 (64, 88)
Psa_pet ≤1 (34)	18	53 (35, 70)
>1 and ≤2 (31)	20	65 (45, 81)
>2 and ≤4 (35)	28	80 (63, 92)
>4 (76)	66	87 (77, 94)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There are three prospective studies for C11 among the 11 articles. Garcia et al. 2009 only has 38 subjects (very small sample size). Richter et al. 2010 does provide clear information on confirmation. The only study with good quality is Breeuswma et al. 2010 study with 70 positive cases. We can not conduct pooled analyses because of the heterogeneity of the studies in terms of patients and data quality.

Breeuswma et al. 010 study included 70 positive cases and 10 controls (true negative), so that the sensitivity and specificity can be evaluated. In the other studies (both prospective studies and retrospective studies), only detection rate (positive scans by PET / total positive cases) can be evaluated because of only positive cases (patients with prostate cancer recurrence were enrolled).

Sensitivity, specificity, PPV, and NPV are not well defined for the Mayo retrospective study. The definition of Truth for sensitivity and specificity analyses is not proper. Therefore, only detection rates were reported by FDA reviewer.

The **detection rate** of C11 PET (positive C11 PET among all enrolled patients) and the 95% exact confidence intervals in percent are 81 (70, 90) from Breeuwsma et al. 2010, 61 (48, 72) from Richter et al. 2010, 68 (51, 82) from Garcia et al. 2009, and 75 (68, 81) from the Mayo clinic retrospective study. The detection rates increase with increasing PSA levels.

Breeuwsma et al. 2010 showed 41/57 patients with positive scan have local recurrence identified of which 26/41 cases were confirmed by biopsy, 15/41 cases by clinical course and PSA response to local salvage treatment. This paper also showed that 16/57 cases had locoregional and or distant recurrence (8 proven by additional CT or MRI, 1 by histological evidence, 6 bone scanning, 1 false positive). Richter 2010 showed 23/43 cases with local recurrence by PET (15 in whole prostate area, 2 in right side, and six in the left) without clear confirmation information. Garcia 2009 showed 14/26 patients detected by C11 present focal uptake of C11, 8 of 14 were confirmed by biopsy, 4 of 14 were confirmed by a reduction in PSA following further radiotherapy, and definitive diagnosis was not reached in 2 of 14 cases.

Mayo clinic retrospective study showed that 34 patients with negative conventional imaging underwent ¹¹C-choline PET/CT and subsequently had biopsies of suspected recurrence sites. The median PSA level of the 34 patients was 3.85 ng/mL (range 0.2 1 to 65.0 ng/mL); 22 of the patients had previously undergone radical prostatectomy and 12 (7 with radiotherapy) had received other therapy (radiotherapy, anti-androgen therapy or cryotherapy). ¹¹C-choline PET/CT images were positive in 30 patients and negative in four patients. Cancer was verified by histopathology in 29 patients; 25 had positive PET/CT images and 4 had negative PET/CT images. Five patients with positive PET/CT images did not have cancer as confirmed with histopathology. In the Mayo study, the median PSA was 4.2 ng/mL (range 0.24 – 65.0 ng/mL)

among the 25 patients with true positive images; PSA levels < 2 ng/mL were observed in four of the nine patients with false negative or false positive images.

5.2 Conclusions and Recommendations

C11 has good detection rate for patients with recurrence of prostate cancer (60% to 80% in prospective studies and 75% in retrospective studies), especially for patients with higher PSA at PET (80% to 90%).

In summary, the applicant's claim about C11 PET is supported by the combined information from the literature research and the study from Mayo clinic. However, there are caveats as noted in the following: 1) The quality of the data from the Mayo clinic is weak (see Section 3.1) especially due to the retrospective study design. 2) The patient-level data of the prospective studies from the literature are not available and so the results of these studies are not inspected.

Therefore, C11 PET should be used only when other conventional imaging approaches fail to identify local or distant disease in patients with recurrent prostate cancer. The exact location of the tumor is not required and is not verified by the submission.

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/s/

LAN HUANG
08/24/2012

JYOTI ZALKIKAR
08/24/2012
I concur with the primary reviewer.

THOMAS E GWISE
08/24/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203155

Applicant: Mayo Clinic PET
Radiochemistry Facility

Stamp Date: December 6,
2011

Drug Name: Choline (C 11)
Injection

NDA/BLA Type: NDA

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	Yes			Yes
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	Yes			Summary of clinical efficacy is in folders \\CDSESUB1\EVSPROD\NDA203155\0000 M2 and M5
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			NA	Efficacy in subpopulations was explored (reported in 2.7.3.4.3). Except analysis by PSA levels, the other subgroup analyses were not explored in detail because of data limitations.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).		No		Have some datasets (without explanations) in M5\53-clin-stud-rep, appendix 7 (pdf file). Do not have the datasets in xpt or sas format. Do not have define.pdf files. According to the report, no safety data were collected.

Request the following information from the sponsor:

- Are the datasets for the pivotal retrospective study available? If the datasets are available, please submit or locate the datasets in xpt or sas format with define.pdf file.
- Submit or locate the summary results from the supporting studies in xpt or sas files.
- Submit or locate the results for subgroup analyses by age.
- Clarify the primary analyses and endpoints including statistical methods and definition of the endpoints. Clarify the success criteria for the primary endpoints.
- Clarify how to handle missing cases or dropouts.
- If it is possible, provide statistical analysis plan.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Review issues:

- There are no analysis datasets for the pivotal retrospective study (in xpt or sas format). There is no define.pdf for the datasets.
- Subgroup analysis results are not complete.
- There is no description on how to conduct the primary analyses. The endpoints are not defined. The success criteria are not stated in the submitted documents.
- There is no description on how to handle missing data or dropouts.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	Y			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.		N		Clinical usefulness not defined, win criteria not clear, no SAP
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			NA	No interim analysis
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			NA	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			NA	No discussion on dropouts. Missing cases are simply excluded.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

There is one retrospective study conducted by the Mayo Clinic PET Radiochemistry Facility.

Study title	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
Choline C 11 positron emission tomography (PET) scan for patients with prostate cancer, with biochemical recurrence following failed initial treatment	Phase N/A, Retrospective, patient chart review; no formal prospective research protocol was performed	1 arm/ 176subjects	Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and clinical usefulness. Win criteria for the primary analyses are not clear.	Effective

There are a total of 11 studies from literatures (shown in the following table).

Study title	Sponsor or authors (year)	Design	Sample size	analyses
Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer.	Rinnab L, Mottaghy FM, Blumstein NM, Reske SN, Hautmann RE, Hohl K, et al. (2007)	Retrospective Single arm	50	Sensitivity, specificity
[(11)C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy.	Rinnab L, Simon J, Hautmann RE, Cronauer MV, Hohl K, Buck AK, et al. (2009)	Retrospective Single arm	41	Sensitivity, specificity, accuracy
[11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy.	Reske SN, Blumstein NM, Glatting G. (2008)	Prospective Two arms (with controls)	49	Sensitivity, specificity, ROC, SUVs
PET/CT with 11C-choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer.	García JR, M. Soler M, Blanch MA, Ramírez I, Riera E, Lozano P, et al. (2009)	Prospective Single arm	38	sensitivity
Detection of local, regional, and distant recurrence in patients with PSA relapse after externalbeam radiotherapy using (11)C-choline positron emission	Breeuwsma AJ, Pruim J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, et al. (2010)	Prospective, single arm	70	Sensitivity, specificity, accuracy, PPV, NPV

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

tomography.				
Is there a role for 11C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/mL.	Castellucci P, Fuccio C, Rubello D Schiavina R, Santi I, Nanni C, et al. (2010)	Retrospective, single arm	102	Sensitivity, specificity, PPV, NPV, ROC, univariate and multivariate binary logistic analysis
Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy.	Giovacchini, G, Picchio M, Coradeschi E, Bettinardi V, Gianolli L, Scattoni V, et al. (2010)	Retrospective, single arm	358	Sensitivity, specificity, PPV, NPV, ROC, Younden's Index, logistic regression
Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment.	Richter JA, Rodríguez M, Rioja J, Peuelas I, Mart-Climent J, Garrastachu P, et al. (2010)	Prospective, single arm	73	sensitivity, specificity, accuracy, PPV, NPV, Fisher exact test, Spearman correlation coefficients
Role of whole-body 18F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer.	Pelosi E, Arena V, Skanjeti A, Pirro V, Douroukas A, Pupi A, et al. (2008)	Retrospective, single arm	56	Sensitivity, student's t test
[18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients.	Cimitan M, Bortolus R, Morassut S, Canzonieri V, Garbeglio A, Baresic T, et al. (2006)	Retrospective, single arm	100	Sensitivity, specificity
Evaluation of [(18)F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging.	Husarik DB, Miralbell R, Dubs M, John H, Giger OT, Gelet A, et al. (2008)	Prospective, single arm	111	Sensitivity, specificity

Note: all the studies except one in this submission are open-label single arm studies without control arm and located in [\CDSESUB1\EVSPROD\NDA203155\0000 M5](#) (5.4).

Lan huang	01/12/2012
Reviewing Statistician	Date
Jyoti Zalkikar	01/12/2012
Supervisor/Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAN HUANG
02/03/2012

JYOTI ZALKIKAR
02/03/2012