CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

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 ADDENDUM

CLINICAL STUDIES

NDA/BLA	NDA 202317
Serial Number:	
Drug Name:	Mechlorethamine hydrochloride
Indication(s):	Stage I (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL), second-line therapy for adults > 18 years
Applicant:	Ceptaris Therapeutics, Inc
Date(s):	Submission Date: 27 February 2013 PDUFA due Date: 27 August 2013 Addendum Date: 25 June 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, Ph.D.
Concurring Reviewers:	Mark Rothmann, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Angelo De Claro, M.D., acting Team leader
Project Manager:	Tyree Newman

Addendum

In this NDA 202317 resubmission, no new clinical data were submitted. Therefore, no further statistical review was performed for this resubmission. Please refer to pervious statistical review dated 19 April 2012 for the original NDA 202317 submission.

Yun Wang, Ph. D.
Mathematical Statistician

Concur: Dr. Rothmann
Cc:
HFD-107/Mr. Newman
HFD-107/Dr. De Claro
HFD-107/Dr. Farrell
HFD-711/Dr. Rothmann
HFD-711/Dr. Sridhara
HFD-700/Ms. Patrician

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/s/

YUN WANG
06/25/2013

MARK D ROTHMANN
06/25/2013
I concur

RAJESHWARI SRIDHARA
06/25/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA	NDA 202317
Serial Number:	
Drug Name:	Mechlorethamine hydrochloride
Indication(s):	Stage I (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL), second-line therapy for adults > 18 years
Applicant:	Yaupon Therapeutics, Inc.
Date(s):	Submission Date: 27 July 2011
	PDUFA due Date: 27 May 2012
	Review Completion Date: 31 March 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Yun Wang, Ph.D.
Concurring Reviewers:	Mark Rothmann, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Office of Hematology and Oncology Product
Clinical Team:	Angelo De Claro, M.D.
	Albert Deisseroth, M.D., Ph.D., Team Leader
Project Manager:	Tyree Newman

Keywords: Cutaneous T-cell lymphoma, mycosis fungoides, non-inferiority, response ratio

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1 EXECUTIVE SUMMARY

Topical nitrogen mustard has been evaluated for the management of mycosis fungoides (MF) for over 5 decades. Topical nitrogen mustard at a concentration of 0.01 – 0.02% is recognized as an effective and conservative outpatient treatment for patients with stage IA, IB, and IIA MF disease.

In the current New Drug Application (NDA) submission, the applicant seeks the approval of Valchor, nitrogen mustard (NM) 0.02% in a propylene glycol (b) (4) (PG), for the second-line treatment of stage I (b) (4) MF for adults (> 18 years). This NDA was based on one pivotal trial, clinical trial 2005NMMF-201-US (Study-201), a randomized, single-blinded (observer-blinded), active-controlled clinical trial of topical mechlorethamine in patients with early stage mycosis fungoides. The primary objective of the study was to evaluate the efficacy of topical application of nitrogen mustard (NM) 0.02% in a propylene glycol ointment (PG) vs. NM 0.02% in an Aquaphor ointment (AP) in subjects with stage I or IIA mycosis fungoides.

The Study-201 met its primary objective of demonstrating non-inferiority on overall response rate of NM 0.02% in PG vs. AP formulation for treating adult (>18 years) patients with stage I or IIA MF. There is a randomization issue described in the clinical study report of the sponsor's submission and this statistical review. The randomization issue did not impact the conclusion of non-inferiority on overall response rate. The data submitted in this application supports the sponsor's claim of efficacy.

2 INTRODUCTION

2.1 Overview

Cutaneous T-Cell Lymphomas (CTCL) are a heterogeneous group of lymphoproliferative diseases characterized by infiltration of the skin by malignant T-cells. CTCL comprise approximately 4% of non-Hodgkin's lymphomas in the United States. Mycosis fungoides (MF), an orphan disease, is the most common presentation.

Nitrogen mustard was the first topical agent with demonstrated efficacy in CTCL. Topical formulations of nitrogen mustard, both aqueous- and ointment-based, in concentrations of 0.01-0.02% have consistently demonstrated efficacy in controlling the progression and symptoms of the cutaneous lesion of MF. Due to instability of aqueous-based solution, since 1980 most patients have received ointment-based nitrogen mustard in Aquaphor. Because there is no FDA-approved topical formulation, patients and physicians are dependent on the services of a limited number of compounding pharmacies, and without the benefit of standardized specifications for

composition and stability. The availability of an FDA-approved product with standardized specifications, suitable stability and wider distribution would respond to a current unmet medical need.

The proposed indication submitted in this NDA application is for the topical treatment of (b) (4) Stage IA, IB (b) (4) mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4) A single pivotal trial, 2005-NMMF-201-US (study 201), was conducted to support the proposed indication. Study 2005-NMMF-201-US was titled "A Phase II pivotal trial to evaluate the safety and efficacy of nitrogen mustard (NM) 0.02% ointment formulations in patients with Stage I or IIA mycosis fungoides (MF)".

Two hundred sixty subjects were randomized and treated between 8 May 2006 and 8 July 2010 from 13 sites in United States. The original protocol was dated 6 January 2006, and the last version was Amendment 5 dated 8 December 2008. The 2005-NMMF-201-US study protocol and the associated Statistical Analysis Plan were submitted to FDA for a Special Protocol Assessment (initial SPA approval, 30 Mar 2007; most recent SPA approval 17 February 2009). The applicant did not provide justification for the non-inferiority threshold in this submission. The non-inferiority threshold of 0.75 for the response rate ratio was specified in the special protocol assessment (SPA). There was agreement with the agency on the SPA. In general, single arm studies have been performed in this disease setting. Historically, response rates have varied from 50% - 85% in the single-arm studies for first line treatment of early stage MF. Not much information was available for second-line treatment of this disease, which is the setting of the submitted trial. Both treatment arms in study 2005-NMMF-201-US contain Nitrogen Mustard, the difference is the delivery formulation.

Throughout this review, patients randomized to receive nitrogen mustard (NM) 0.02% in a propylene glycol ointment are referred as "PG (Yaupon)" arm in the text, tables/figures, whereas patients randomized to receive NM 0.02% in an Aquaphor ointment are referred as "AP (control)" arm in the text, the tables/figures.

Table 1: List of all studies included in analysis

Study	**Phase and Design**	**Treatment Period**	**Follow-up Period**	**# of Subjects per Arm**	**Enrollment period** **Geographic region**
2005-NMMF-201-US	Phase II, randomized (1:1), single-blinded, multicenter study of PG vs. AP for the treatment of patients with stage I, IIA MF.	12-month treatment unless disease progression, treatment limiting toxicity, concomitant illness, or	Patients were followed off study for an additional 12 months to assess the potential for the development of cutaneous tumors, in particular	PG(Yaupon) (N=130) AP(Control) (N=130)	8 May 2006–8 July 2010 13 sites in: United States

	other change in health status necessitated discontinuation of study therapy.	squamous cell carcinoma.	

2.2 Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\Fdswa150\nonectd\N202317\N_000\2011-07-27

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the pivotal study 2005-NMMF-201-US.

3.1 Data and Analysis Quality

The efficacy endpoints (CAILS response, SWAT response etc) were derived and saved in analysis dataset "XEF". This NDA submission has provided all source data for the tumor assessment and the rule for defining response. The statistical reviewer checked and verified that the derived efficacy analysis datasets could be reproduced from the NDA tabulation datasets.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Efficacy Endpoints

3.2.1.1 Study Design

The pivotal trial 2005-NMMF-201-US, is a single-blinded (observer-blinded), randomized, multi-center study of topical mechlorethamine in patients with early stage mycosis fungoides. At the pre-study visit (which occurred up to 90 days before baseline [Day 1]), patients were screened for eligibility, including a skin biopsy to confirm diagnosis of Stage IA, IB or IIA MF. All patients had to have received at least one prior skin-directed therapy for MF such as corticosteroids, PUVA, UVB, or Targretin, but not topical NM within the last two years or topical carmustine (BCNU). After eligibility was confirmed, patients were stratified into two groups by their MF stage: Stage IA vs. IB, IIA, and were then randomized at 1:1 ratio to receive 0.02% NM in either PG or AP formulation. The randomization was done separately at each site by personnel (site pharmacist or study coordinator not involved in patient assessment) who were not blinded to treatment; patients were randomized at a blocks of 10 (it was estimated that each site would accrue 20 or more patients). Approximately 250 patients were planned to be enrolled in the study.

The primary objective of the study 2005-NMMF-201-US was to evaluate the efficacy of topical application of nitrogen mustard (NM) 0.02% in a propylene glycol ointment (PG) vs. NM 0.02% in an Aquaphor ointment (AP) in subjects with stage I or IIA MF. The primary efficacy endpoint was the Composite Assessment of Index Lesion Severity (CAILS) response within up to 12 months of study drug application. Final efficacy analyses were planned after the last patient received 12-month treatment. No interim analysis was planned or conducted.

The significance level α for the final analysis of CAILS response was 0.05 (2-sided). Non-inferiority will be assessed based on the 95% confidence interval (CI) for CAILS response rates ratio for PG vs. AP formulation. Non-inferiority of PG formulation to the AP formulation would be demonstrated if the lower limit of the 95% confidence interval of CAILS response rate ratio (PG vs. AP) is ≥ 0.75.

To provide at least 80% power to demonstrate non-inferiority, it was estimated that 240-250 patients should be randomized into the study.

Reviewer's comment:

Patients were screened for eligibility and randomized to treatment arms up to 90 days before the baseline visits. Patients' disease status was reassessed at the Baseline visit (Day 1). If disease status was upgraded from Stage IA to IB or IIA, they were re-randomized; if disease progressed beyond Stage IIA, they were withdrawn from the trial prior to receiving any study treatment.

3.2.1.2 Efficacy Endpoints

The primary efficacy endpoint was the Composite Assessment of Index Lesion Severity (CAILS) response within up to 12 months of study drug application. The response should be confirmed by two or more consecutive observations over at least 4 weeks. CAILS score was obtained by adding the severity score of each of the following symptoms for up to 5 index lesions: erythema, scaling, plaque elevation, and surface area. Severity was scored from 0 (none) to 8 (severe) for erythema and scaling, from 0-3 for plaque elevation and 0-9 for surface area. A complete response (CR) was defined as a CAILS score of 0. A partial response was defined as ≥ 50% decrease from baseline in CAILS score. If patients did not achieve a response, their last CAILS score was compared with the baseline value. If the CAILS score increased by ≥ 25%, they were categorized as "Progression Disease", otherwise they were categorized as "Stable Disease".

The secondary efficacy endpoints included:

- Severity Weighted Assessment Tool (SWAT) response within up to 12 months of study drug application; SWAT score was derived by measuring each involved area as a percentage of total body surface area (%BSA) and multiplying it by a severity-weighting factor (1=patch, 2=plaque, 3=tumor); SWAT response was similarly defined as CAILS response, and also needed to be confirmed by two or more consecutive observations over at least 4 weeks.
- Time to CAILS response

- Duration of CAILS response
- CAILS time to progression (25% increases from baseline CAILS score).

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Analysis population

The intent-to-treat (ITT) population was defined as all randomized subjects. Subjects were analyzed by the treatment arm they were assigned to at final randomization. ITT population was the primary analysis population for all efficacy analyses, and was used for descriptions of disposition, demographics, and baseline disease characteristics.

The safety population was defined as all randomized subjects who received at least one dose of study treatment (0.02% NM in PG or AP formulation). Of the 260 subjects randomized, 5 subjects (2 from PG arm and 3 from AP arm) did not receive study treatment. Four patients (2 in PG arm: 001-0001, 002-0051, 2 in AP arm: 002-0024, 002-0040) had disease progressed between screening and baseline and were no longer eligible for the trial. One additional patient randomized to AP arm withdrew consent prior to starting study medication because it was too far to travel.

Subject accrual

Study 2005-NMMF-201-US randomized 260 subjects, 130 to PG arm and 130 to the AP arm respectively, from 13 sites in United States. Table 2 summarizes the study accrual by site.

Table 2: Study accrual by site, ITT population

Site	**PG (Yaupon) N=130 n (%)**	**AP (Control) N=130 n (%)**
Center 1: Brigham & Women's Hospital	3 (2.3)	1 (0.8)
Center 2: MD Anderson Cancer Center	30 (23.1)	32 (24.6)
Center 3: Stanford University	20 (15.4)	18 (13.8)
Center 4: Fox Chase Cancer Center	8 (6.2)	7 (5.4)
Center 5: Duke University	8 (6.2)	10 (7.7)
Center 6: Hospital of the University of Penn.	4 (3.1)	3 (2.3)
Center 7: New York University	11 (8.5)	7 (5.4)
Center 8: Oklahoma University	1 (0.8)	6 (4.6)
Center 9: Columbia University	5 (3.8)	4 (3.1)
Center 10: Northwestern University	22 (16.9)	22 (16.9)
Center 11: Utah Clinical Trials	7 (5.4)	7 (5.4)
Center 12: University of Texas Southwestern	10 (7.7)	11 (8.5)
Center 13: University of Wisconsin	1 (0.8)	2 (1.5)

[Source: study 2005-NMMF-201-US clinical study report (CSR) Page 78 Table 30]

Reviewer's comment:

Study coordinator at NYU violated randomization rule and did not use the randomization codes; patients were assigned to treatment based on MF stage. Eighteen subjects enrolled at NYU were excluded from ITT population for further analysis, that population is referred as ITT population excluding NYU.

Subject disposition

Patients were treated on this trial for 12 months unless disease progression, treatment limiting toxicity, concomitant illness, or other change in health status necessitated discontinuation of study therapy. Patients were followed off study for an additional 12 months to assess the potential for the development of cutaneous tumors, in particular squamous cell carcinoma. During this 12-month follow-up period, patients who had not achieved a complete response on either the PG or AP formulation of topical nitrogen mustard 0.02% could enroll in the open label 7-month trial of the PG formulation containing 0.04% nitrogen mustard (protocol 2007NMMF-202-US).

At the time of 8 July 2010, all patients had discontinued study treatment. The most common reason for discontinuation in both arms was "completed 12 months study treatment" (65.5% in

the PG arm and 67.5% in the AP arm, respectively). The second most common reason for treatment discontinuation was treatment limiting toxicity (15.1% in the PG arm and 12.2% in the AP arm, respectively). The third most common reason for treatment discontinuation was other adverse event (3.4% in the PG arm and 5.0% in the AP arm, respectively), as shown in Table 3.

Table 3: Subject disposition, ITT population excluding NYU

	PG (Yaupon) (N=119) n (%)	**AP (Control) (N=123) n (%)**
All randomized	119 (100)	123 (100)
Never Treated	2 (1.7)	3 (2.4)
Treated	117 (98.3)	120 (97.6)
Withdrawn prior to completing 12 months study Rx	39 (32.8)	37 (30.1)
Completed 12 months Study Rx	78 (65.5)	83 (67.5)
Reasons for discontinuation		
Treatment limiting toxicity	18 (15.1)	15 (12.2)
Other Adverse event	4 (3.4)	6 (5.0)
Lack of efficacy	4 (3.4)	3 (2.4)
Concurrent illness	4 (3.4)	3 (2.4)
Lost to follow-up	2 (1.7)	3 (2.4)
Withdrew consent	2 (1.7)	1 (0.8)
Non-compliance	1 (0.8)	3 (2.4)
Subject's best interest	1 (0.8)	0 (0.0)
Other	3 (2.5)	3 (2.4)

[Source: study 2005-NMMF-201-US CSR Pages 42 – 43 Table 3 and Table 4]

Reviewer's comment:

In the study 2005-NMMF-201-US CSR Table 3 of the sponsor's submission, subjects who never received study treatment were counted in "Treatment discontinued" category. In the above Table 3 in this review document, these patients are excluded from "Treatment discontinued" category.

Subject demographics and baseline disease characteristics

Subject demographics appeared to be balanced between the PG arm and the AP arm (Table 4). Baseline disease characteristics are summarized in Table 5, and appeared to be balanced between two treatment arms as well.

Table 4: Demographics, ITT population excluding NYU

	PG (Yaupon) (N=119)	**AP (Control) (N=123)**
Age (years)		
Mean (SD)	54.4 (14.5)	56.4 (14.5)
Median	57	58
Range	(24, 83)	(11, 88)
Category, n (%)		
< 18	0 (0.0)	1 (0.8)
18 – 64	85 (71.4)	81 (65.9)
65 – 74	27 (22.7)	32 (26.0)
≥ 75	7 (5.9)	9 (7.3)
Sex, n (%)		
Male	71 (59.7)	72 (58.5)
Female	48 (40.3)	51 (41.5)
Race, n (%)		
White	89 (74.8)	92 (74.8)
Black	15 (12.6)	17 (13.8)
Other	15 (12.6)	14 (11.4)

SD: standard deviation;
[Source: Study 2005-NMMF-201-US CSR Page 60 Table 10a]

Table 5: Baseline disease characteristics, ITT population excluding NYU

	PG (Yaupon) (N=119)	AP (Control) (N=123)
Baseline MF stage, n (%)		
Stage IA	65 (54.6)	64 (52.0)
Stage IB	52 (43.7)	57 (46.3)
Stage IIA	2 (1.7)	2 (1.6)
Baseline CAILS score		
Mean (SD)	38.0 (17.2)	37.1 (17.8)
Median	36	33
Range	(2, 79)	(6, 87)
Baseline SWAT score		
Mean (SD)	15.1 (16.2)	18.2 (19.2)
Median	9	11
Range	(1, 104)	(1, 104)
Baseline BSA		
Mean (SD)	12.7 (12.0)	15.6 (15.2)
Median	8.5	9
Range	(1, 61)	(1, 76)

CAILS: Composite Assessment of Index Lesion Severity; SWAT: Severity Weighted Assessment Tool; BSA: Body Surface Area; SD: standard deviation.

[Source: Study 2005-NMMF-201-US CSR Pages 60 Tables 10a]

Stage migration from randomization to baseline visit

Randomization was stratified by MF stage (stage IA vs. IB or IIA). Patients were screened for eligibility and randomized to treatment arms up to 90 days before the baseline visits. Patients' disease status was reassessed at the Baseline visit (Day 1). Twenty-three of the 242 patients (7 in PG arm, 16 in AP arm) had a change in MF stage between screening and baseline visit, 5 patients (2 in PG arm and 3 in AP arm) had MF disease progressed beyond stage IIA and were no longer eligible for the study. Two patients had MF stage changed from IIA to IB which not affected randomization strata. Sixteen patients had a change in MF stage which resulted in change in randomization strata, 8 subjects were re-randomized and the other 8 remained with the original randomization.

Protocol violation

All 18 patients from NYU (11 [8.5%] in the PG arm and 7 [5.4%] in the AP arm) were considered as having a major protocol violation. In addition, 19 subjects [7.9%] (12 [10.1%] in the PG arm and 7 [5.7%] in the AP arm) had protocol violations defined as selection criteria not met (disease progressed beyond IIA at baseline) and use of prohibited concomitant medication (Table 6).

Table 6: Subjects with major protocol deviations, ITT population excluding NYU

	PG (Yaupon) (N=119) n (%)	**AP (Control) (N=123) n (%)**
Total No. subjects with major protocol deviation	12 (10.1)	7 (5.7)
Disease stage beyond IIA	2 (1.7)	3 (2.4)
Prohibited concomitant medication	10 (8.4)	4 (3.3)

[Source: Study 2005-NMMF-201-US CSR Page 47 – 56 Tables 5, 6, 7]

3.2.3 Statistical Methodologies

The number and percentage of subjects with CAILS (SWAT) response will be summarized by treatment group. Using the likelihood based methods of Miettinen and Nurminen, an estimate of ratio of CAILS response rates along with its 95% confidence limit will be calculated for the ITT population excluding NYU. If the lower 95% confidence limit is greater than 0.75 then it will be concluded that by using the ratio of response rates, the 0.02% NM in the PG formulation is non-inferior to the AP formulation.

The secondary endpoint, SWAT response was analyzed using the same method as for CAILS response. Time to CAILS response, duration of CAILS response, and time to CAILS progression were summarized by Kaplan-Meier method.

The number and percentage of subjects with CAILS response will also be summarized for each treatment group by subject age, gender, race, and disease stage.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy analysis results

The analysis results of primary endpoint of CAILS response and secondary endpoint of SWAT response are summarized in Table 7 and Table 8 respectively.

Table 7: CAILS response – ITT population excluding NYU

	PG (Yaupon) (N=119) n (%)	**AP (Control) (N=123) n (%)**	**Response ratio (95% CI)**
Response	**71 (59.7)**	**59 (48.0)**	1.24
Complete response	17 (14.3)	14 (11.4)	(0.98, 1.58)
Partial response	54 (45.4)	45 (36.6)	
Non-response	**48 (40.3)**	**64 (52.0)**	
Stable disease	36 (30.3)	59 (48.0)	
Progressive disease	5 (4.2)	1 (0.8)	
Unevaluable	7 (5.9)	4 (3.3)	

CI: Confidence interval.

[Source: Study 2005-NMMF-201-US CSR Page 63 Table 13]

Table 8: SWAT response – ITT population excluding NYU

	PG (Yaupon) (N=119) n (%)	**AP (Control) (N=123) n (%)**	**Response ratio (95% CI)**
Response	**59 (49.6)**	**57 (46.3)**	1.07
Complete response	8 (6.7)	4 (3.2)	(0.82, 1.39)
Partial response	51 (42.9)	53 (43.1)	
Non-response	**60 (50.4)**	**66 (53.7)**	
Stable disease	43 (36.1)	45 (36.6)	
Progressive disease	11 (9.2)	17 (13.8)	
Unevaluable	6 (5.0)	4 (3.3)	

CI: Confidence interval;

[Source: Study 2005-NMMF-201-US CSR Page 72 Table 19]

Reviewer's comment:

- The observed CAILS response rates ratio was 1.24 with lower 95% confidence limit of 0.98, which was greater than the pre-specified non-inferiority threshold of 0.75.
- The SWAT analysis results were consistent with CAILS results in supporting non-inferiority of PG formulation to AP formulation.

Table 9 and 10 summarize time to CAILS response and duration of CAILS response.

Table 9: Time to CAILS response – ITT population excluding NYU

Time to CAILS response	**PG (Yaupon) (N=119)**	**AP (Control) (N=123)**
Number of Responses	71	59
Median Time to Response, months (95% CI)	3.8 (3.0, 5.1)	3.2 (2.5, 4.2)

CI: Confidence interval;

[Source: Statistical reviewer's analysis]

Table 10: Duration of CAILS response – responders only

Duration of CAILS response	**PG (Yaupon)**	**AP (Control)**
Number of subjects with Responses	71	59
Number progressed	11	11
Censored	60	48
Median Duration Response, months (95% CI)	11.5 (11.5, NE)	NE (NE, NE)

CI: Confidence interval; NE: not evaluable.

[Source: Statistical reviewer's analysis]

Reviewer's comment:

CAILS Time to progression (TTP) analysis results were not presented in this statistical review since the results are difficult to interpret due to the reason that CAILS TTP was limited to assessment of progression in index lesions, and progression in non-index lesions or new lesions were not captured.

3.2.4.2 Conclusions for efficacy

The pivotal study 2005-NMMF-201-US met the primary objective of demonstrating non-inferiority on overall response rate for 0.02% NM in PG formulation vs. AP formulation by yielding a lower 95% confidence limit of 0.98 for CAILS response rates ratio for the PG arm versus the AP arm. The analysis results of the secondary endpoint of SWAT response were consistent with the primary analysis results and supported non-inferiority claim.

3.3 Evaluation of Safety

Please refer to clinical review of this application for safety results and conclusions for safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, MF stage

Table 11 summarizes the subgroup analyses of CAILS response by gender, race, age, and disease stage for the study 2005-NMMF-201-US. All patients were from US and therefore a regional analysis was not conducted.

Reviewer's comment:

- Except for Race "Other", age "≥ 65 years" and MF stage "IB, IIA" categories, subgroup analyses results were consistent with the primary analysis results of non-inferiority in CAILS response rates ratio for PG formulation vs. AP formulation.

Table 11: Subgroup analysis of CAILS response – ITT excluding NYU

Subgroup	**PG (Yaupon) (N=119) Response/n (%)**	**AP (Control) (N=123) Response/n (%)**	**Response Ratio (95% CI)**
Gender			
Male	40/71 (56.3)	33/72 (45.8)	1.23 (0.89, 1.71)
Female	31/48 (64.6)	26/51 (51.0)	1.27 (0.90, 1.81)
Race			
White	52/89 (58.4)	43/92 (46.7)	1.25 (0.95, 1.66)
Black	10/15 (66.7)	7/17 (41.2)	1.62 (0.83, 3.33)
Other	9/15 (60.0)	9/14 (64.3)	0.93 (0.50, 1.73)
Age			
≤ 64 yrs	56/85 (65.9)	42/82 (51.2)	1.29 (0.99, 1.69)
≥ 65 yrs	15/34 (44.1)	17/41 (41.5)	1.06 (0.62, 1.80)
MF stage			
IA	40/65 (61.5)	26/64 (40.6)	1.51 (1.07, 2.19)
IB, IIA	31/54 (57.4)	33/59 (55.9)	1.03 (0.74, 1.42)

[Source: Statistical reviewer's analysis]

5 SUMMARY AND CONCLUSIONS

In the current NDA submission, the applicant seeks the approval of 0.02% NM in PG formulation for the treatment of patients with Stage I (b) (4) MF. The pivotal trial 2005-NMMF-201-US is a randomized, single-blinded, multi-center study of active-controlled clinical trial of topical mechlorethamine in patients with early stage MF. This study enrolled a total of 260 subjects from 13 sites in United States. The primary efficacy endpoint was CAILS response.

The study 2005-NMMF-201-US demonstrated non-inferiority in CAILS and SWAT response rates ratio for PG arm versus AP arm with lower 95% confidence limit greater than 0.75.

5.1 Statistical Issues and Collective Evidence

There was a randomization issue at NYU site, where the patients were randomized to treatment arm based on disease stage, not by randomization codes. All patients from NYU were excluded from further analyses. That randomization issue did not impact the determination of non-inferiority on overall response rate for PG formulation vs. AP formulation.

5.2 Conclusions and Recommendations

This NDA application was based on a multicenter, randomized trial (2005-NMMF-201-US) comparing 0.02% nitrogen mustard in a propylene glycol ointment formulation versus aquaphor ointment formulation for the second-line treatment of adult patients (>18 years) with stage I or IIA mycosis fungoides. The trial showed non-inferiority on overall response rate for PG formulation vs. AP formulation. The statistical results support the efficacy claim in the primary endpoint of CAILS response.

6 SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Yun Wang, Ph.D.
Date: March 31, 2012

Concurring Reviewer(s):

Statistical Team Leader: Mark Rothmann, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:
Project Manager: Tyree Newman
Medical Officer: Angelo De Claro, M.D.
Medical Team Leader: Albert Deisseroth, M.D.
Hematology Product Division Director: Ann Farrell, M.D.
Primary Statistical Reviewer: Yun Wang, Ph.D.
Statistical Team Leader: Mark Rothmann, Ph.D.
Biometrics Division Director: Rajeshwari Sridhara, Ph.D.
Lillian Patrician

c:\NDA\statreview.doc

7 CHECK LIST

Number of Pivotal Studies: 1

Trial Specification

Specify for each trial:

Protocol Number (s): 2005-NMMF-201-US

Protocol Title (optional): A Phase II pivotal trial to evaluate the safety and efficacy of nitrogen mustard (NM) 0.02% ointment formulations in patients with Stage I or IIA mycosis fungoides (MF)

Phase: II

Control: Active Control

Blinding: Open-Label

Number of Centers: 13

Region(s) (Country): United States

Duration: 50 months

Treatment Arms: Topical application of nitrogen mustard (NM) 0.02% in a propylene glycol ointment (PG) vs. NM 0.02% in an Aquaphor ointment (AP)

Treatment Schedule:

PG arm: 0.02% gel, topical once daily

AP arm: 0.02% gel, topical once daily

Randomization: Yes

Ratio: 1:1

Method of Randomization: stratified, blocked randomization by personnel in each site

If stratified, then the Stratification Factors:

MF disease stage (Stage IA vs. IB or IIA)

Primary Endpoint: CAILS response

Primary Analysis Population: ITT

Statistical Design: non-inferiority

Adaptive Design: No

Primary Statistical Methodology: likelihood based methods of Miettinen and Nurminen

Interim Analysis: No

Sample Size: 260

Sample Size Determination: based on the primary endpoint CAILS response

Statistic = likelihood ratio

Power= 80%

Non-inferiority threshold = 0.75 for lower 95% confidence interval for CAILS response rates ratio of PG vs. AP arm

α = 0.05 (2-sided)

- Was there an **Alternative Analysis** in case of violation of assumption; e.g., Lack of normality, Proportional Hazards Assumption violation. No.
- Were there any major changes, such as changing the statistical analysis methodology or changing the primary endpoint variable? No.
- Were the **Covariates** pre-specified in the protocol? No.
- Did the Applicant perform **Sensitivity Analyses**? No.
- How were the **Missing Data** handled? Unevaluable patients were treated as non-responders.
- Was there a **Multiplicity** involved? No.
- **Multiple Secondary Endpoints**: Are they being included in the label? If yes, method to control for type 1 error. No.

Were Subgroup Analyses Performed (Yes/No)? Yes.

- Were there any **Discrepancies** between the protocol/statistical analysis plan vs. the study report? No.
- Overall, was the study positive (Yes/No)? Yes.

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/s/

YUN WANG
04/18/2012

MARK D ROTHMANN
04/19/2012

RAJESHWARI SRIDHARA
04/19/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202317 **Applicant:** Yaupon Therapeutics, Inc. **Stamp Date:**

Drug Name: Nitrogen Mustard **NDA/BLA Type:** 505(b)(2)

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.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

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.

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.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Comment: please provide justification for non-inferiority margin used in the study 2005NMMF-201-US.

Yun Wang **31Aug2011**

Reviewing Statistician Date

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

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/s/

YUN WANG
09/02/2011

MARK D ROTHMANN
09/02/2011