CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202317Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	202317
Priority or Standard	Class 2 Resubmission
Submit Date(s)	27 February 2013
Received Date(s)	27 February 2013
PDUFA Goal Date	27 August 2013
Division / Office	DHP / OHOP
Reviewer Name(s)	R. Angelo de Claro, M.D.
Review Completion Date	25 June 2013
Established Name	Mechlorethamine
(Proposed) Trade Name	Valchlor
Therapeutic Class	Antineoplastic
Applicant	Ceptaris Therapeutics, Inc.
Formulation(s)	0.016% gel
Dosing Regimen	Topical, once daily
Indication(s)	CTCL Stage IA and IB, second-line therapy
Intended Population(s)	Adults ≥ 18 years

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend regular approval for this 505(b)(2) application (NDA 202317).

1.2 Risk Benefit Assessment

The clinical reviewer finds a favorable benefit-risk profile for topical nitrogen mustard (mechlorethamine) for the indication: (b) (4) The primary basis for approval was clinical trial 2005NMMF-201-US, a randomized, active-controlled, observer-blinded, multicenter clinical trial that enrolled 260 patients from 13 sites in the United States.

- The efficacy results in clinical trial 2005NMMF-201-US demonstrated a CAILS response rate of 60% in the Valchlor arm and 48% in the control arm. Clinical trial 2005NMMF-201-US achieved its primary endpoint for non-inferiority; the CAILS response rate ratio was 1.24 with 95%CI of 0.98 to 1.58. Secondary efficacy endpoints supported the primary endpoint result which include:
  - The SWAT response rate ratio was 1.07 with 95%CI of 0.82 to 1.39. The SWAT response rate was 50% in the Valchlor arm, and 46% in the control arm.
  - Time to CAILS response and time to SWAT response were similar between treatment arms. Median time to response (CAILS or SWAT) was 4 months for the Valchlor arm, and 3 months for the control arm.

- The safety profile of topical mechlorethamine was adequately described in the results of clinical trial 2005NMMF-201-US. The most common adverse event was dermatitis, a known adverse event with topical mechlorethamine therapy. Dermatitis was reported in 57% of patients in the Valchlor arm and 58% in the control arm. Moderately-severe or severe dermatitis was reported in 23% of patients in Valchlor arm and 17% in control arm. Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial.

- Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up.

Below is a separate analysis which was carried out using the Benefit-Risk Assessment Framework Tool. This analysis is provided below in Table 1.

Table 1 Benefit-Risk Analysis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF-type CTCL Stage IA, IB (b) (4)	The condition is an orphan indication that would be considered serious given the cutaneous symptoms associated with the disease. However, the condition is associated with a chronic course with overall survival comparable to an age-matched population.	MF-type CTCL Stage IA, IB (b) (4) is a serious medical condition that is debilitating and would lead to chronic morbidity.
Unmet Medical Need	Skin-directed therapies for MF (from 2011 NCCN guidelines) include topical corticosteroids, topical chemotherapy, radiation therapy, topical retinoids, phototherapy. Of these therapies, topical Targretin is the only FDA-approved therapy for the condition. The Targretin approval was based on an ORR of 26%.	An approved therapy exist (topical Targretin); but of limited efficacy (ORR 26%). Hence, there remains an unmet medical need for other therapies for the condition.
Clinical Benefit	Efficacy results from a single, randomized, active-controlled, observer-blinded trial demonstrated a CAILS response rate of 60% in the Valchlor arm. SWAT response rate was 50% in Valchlor arm.	The applicant's results were verified on analysis of the raw data. OSI inspections of the clinical site data concluded that data were reliable. The evidence for clinical benefit is acceptable and supports regular approval.
Risks	The safety profile is notable for development of dermatitis (any grade 57%, moderately-severe or severe 23%), a known adverse reaction of topical nitrogen mustard therapy. Also, 11 of 255 patients treated with topical nitrogen mustard (4%) developed non-melanoma skin cancer during the course of the clinical trial or during long-term follow-up.	The safety risks of dermatitis and development of secondary skin cancers are well-known adverse reactions for topical nitrogen mustard therapy. The clinical trial adequately characterized the risks of dermatitis and secondary skin cancers.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The applicant proposed a REMS assessment plan which included a medication guide (b) (4)	The medication guide (b) (4) may be implemented outside of a REMS assessment plan. Hence, a REMS assessment plan is not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a REMS assessment plan which includes a medication guide (b) (4) I agree with the proposed medication guide as this would provide for detailed instructions to the patient and the patient's caregiver regarding the appropriate and safe use of the product. However, I disagree with the Applicant's proposal that the medication guide would need to be under a REMS assessment plan. The use of topical nitrogen mustard has been described since the 1950s, and there is extensive literature describing the use of topical nitrogen mustard (mechlorethamine) for the proposed indication. In addition, the anticipated prescribers for this medication would mostly consist of specialists (e.g., oncologist, dermatologist) and multi-disciplinary teams with expertise in the treatment of cutaneous T-cell lymphoma.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

Refer to original clinical review.

Topical nitrogen mustard (mechlorethamine) has been evaluated for the management of mycosis fungoides (MF) since the 1950s, predominantly through retrospective analysis of medical records. Prior to the clinical trial in the application, there have been no randomized clinical trials with nitrogen mustard for the management of MF.

Reviewer Comment: The terms "nitrogen mustard" and "mechlorethamine" are used interchangeably in this review.

The major toxicity of topical nitrogen mustard is allergic contact dermatitis, which has been reported to occur in 35-70% of patients and often results in discontinuation of therapy.

For this 505(b)(2) New Drug Application for marketing authorization of the Applicant's proprietary formulation containing mechlorethamine hydrochloride, Mustargen® will be used as the Reference Listed Drug (RLD). The Applicant is proposing to accept sections of the current labeling language for Mustargen® including Warnings for the Use of the Product (modified for the Ceptaris topical product), Carcinogenesis, Mutagenesis, Impairment of Fertility, Usage in Pregnancy, and Pregnancy Category.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical module component of this resubmission is adequate for review.

3.2 Compliance with Good Clinical Practices

Clinical trial 2005NMMF-201-US was previously inspected during the first review cycle. Refer to Clinical Inspection Summary from the Office of Scientific Investigations (OSI) dated March 26, 2012. OSI concluded that "Based upon review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication".

The Applicant submitted updated safety information regarding clinical trial 2005NMMF-201-US as a presubmission. Re-inspection of 2005NMMF-201-US was not required for this resubmission.

3.3 Financial Disclosures

In accordance with 21 CFR 54.4, the Applicant submitted the required financial disclosure requirements and certification during the first review cycle.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See CMC review.

4.2 Clinical Microbiology

Refer to Microbiology review.

4.3 Preclinical Pharmacology/Toxicology

Refer to Pharmacology-Toxicology review.

4.4 Clinical Pharmacology

Refer to Clinical Pharmacology review.

5 Sources of Clinical Data

No additional clinical trials were conducted for the proposed indication to support this resubmission. Refer to original clinical review for the details on clinical trial 2005NMMF-201-US.

Module 5 of this resubmission included 2 published references. The Applicant had previously submitted datasets and additional case report forms (NDA 202317 SDN 31 Received 7/26/2012) to support the re-analysis of duration of follow-up for adverse events.

5.1 Tables of Studies/Clinical Trials

Refer to original clinical review.

5.2 Review Strategy

Refer to original clinical review.

5.3 Discussion of Individual Studies/Clinical Trials

Refer to original clinical review.

6 Review of Efficacy

Efficacy Summary

The efficacy of Valchlor was evaluated in 242 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key efficacy results from this non-inferiority clinical trial are listed below.

- The primary endpoint was CAILS response (based on maximum of 5 index lesions per patient). Secondary endpoints include SWAT response (global response), duration of CAILS response, time to CAILS response, and time to CAILS progression. Non-inferiority to active control would be demonstrated if the lower limit of the 95% confidence interval of response rate ratio (Valchlor:control) is $\geq$ 0.75.

- Clinical trial 2005NMMF-201-US achieved its primary endpoint. The CAILS response rate ratio was 1.24 with 95%CI of 0.98 to 1.58. The CAILS response rate was 60% in Valchlor arm and 48% in control arm.

- Secondary endpoints supported the primary endpoint result.
  – The SWAT response rate ratio was 1.07 with 95%CI of 0.82 to 1.39. The SWAT response rate was 50% in the Valchlor arm, and 46% in the control arm.
  – Time to CAILS response and time to SWAT response were similar between treatment arms. Median time to response (CAILS or SWAT) was 4 months for the Valchlor arm, and 3 months for the control arm.

- The trial population consisted of 242 patients enrolled from U.S. sites. Patients were required to have central and local pathology confirmation of the diagnosis of mycosis fungoides. All patients had at least one prior therapy. There was similar distribution of demographic parameters (gender, age, race) and baseline disease characteristics (stage of disease, duration of disease, prior therapies) between treatment arms.

The CR resubmission did not contain additional efficacy data. Refer to original clinical review for efficacy analysis.

7 Review of Safety

Safety Summary

The safety of Valchlor was evaluated in 255 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key safety results from this clinical trial are listed below.

- Topical mechlorethamine was applied once daily. The duration of treatment was similar between treatment arms with a median of approximately 52 weeks. Fifty-five percent of patients required suspension of treatment or reduction of dose frequency during the clinical trial.

- The most common adverse event was dermatitis, a known adverse event with topical mechlorethamine therapy. Dermatitis was reported in 57% of patients in the Valchlor arm and 58% in the control arm. Moderately-severe or severe dermatitis

was reported in 23% of patients in Valchlor arm and 17% in control arm. Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial.

- Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up. Eight patients developed nMSC during treatment with topical mechlorethamine. Risk factors associated with development of nMSC include age $\geq$ 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).

7.1 Methods

Refer to original clinical review.

7.2 Adequacy of Safety Assessments

Refer to original clinical review.

7.3 Major Safety Results

Refer to original clinical review.

The resubmission provided for clarification of the duration of follow-up of patients for adverse events, including follow-up for secondary skin cancers. The median duration of follow-up for AEs was 370 days (IQR 274;407 days) in the PG group (Valchlor)(N=128). The median duration of follow-up for AEs was 367 days (IQR 292;407 days) in the control group(N=127).

8 Postmarket Experience

Valchlor is not marketed in the United States.

9 Appendices

9.1 Literature Review/References

Refer to original clinical review.

9.2 Labeling Recommendations

Section 1: Indications and Usage
- Add modifier to indication "who have received at least one prior skin-directed therapy" to reflect actual population enrolled in clinical trial. (b) (4)

Section 2: Dosage and Administration
- Change to active voice, revise to improve clarity of instructions.

Section 5: Warnings and Precautions
- Change to active voice, and make language more concise (b) (4)

Section 6: Adverse Reactions
- Recommend to include all adverse reactions regardless of attribution because patients were not blinded to study treatments. Also, regardless of attribution, patients experienced the adverse events, and hence, should be described in the prescribing information. Because the indication is for an early stage disease with prolonged survival, a cut-off of ≥5% adverse events is recommended.

Section 8: Use in Specific Populations
- Include actual percentages of geriatric patients who experienced dermatitis as compared to non-geriatric patients.

Section 14: Clinical Studies
- Add brief paragraph regarding description of patient population.
- Add SWAT response to efficacy results, and description of SWAT response.
- Recommend to include information regarding low rate of complete responses (CR) on CAILS or SWAT criteria. Published literature cites 60-70% CR rates with topical mechlorethamine based on retrospective data.

(b) (4)

Section 15: References
- Revise to only include standard references.

Section 17: Patient Counseling Information
- Change language to active voice. Make language more concise.

9.3 Advisory Committee Meeting

The application was not taken to Oncologic Drugs Advisory Committee.

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/s/

ROMEO A DE CLARO
06/25/2013

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Acting Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	202317
Applicant Name	Ceptaris Therapeutics, Inc.
Date of Submission	7/27/11
PDUFA Goal Date	5/27/12
Proprietary Name / Established (USAN) Name	Valchor/Nitogen Mustard Gel 0.02%
Dosage Forms / Strength	0.02% Topical Gel
Proposed Indication(s)	For the treatment of Mycosis Fungoides (CTCL (b) (4)
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Angelo DeClaro, M.D./Albert Deisseroth, M.D./Ph.D.
Statistical Review	Qing Xu, Ph.D./Mark Rothmann, Ph.D.
Pharmacology Toxicology Review	Yash Chopra, PhD./ Haleh Saber, Ph.D.
CMC Review/OBP Review	Anne Marie Russell, Ph.D./Janice Brown, M.S.
Microbiology Review	Stephen E. Langille, Ph.D./Bryan Riley, Ph.D.
Clinical Pharmacology Review	Rachelle Lubin, Ph.D./Julie Bullock, Pharm.D.
DDMAC	James Dvorsky
DSI	Anthony Orencia, M.D.
CDTL Reviews	Albert Deisseroth, M.D., Ph.D.
OSE/DMEPA	
OSE/Epidemiology	
OSE/DRISK	
Other - statistical safety	
Other – Pediatrics Maternal Health Team Other- Pharmacometrics	

Signatory Authority Review Template

1. Introduction

Cepatris has submitted a 505 b2 application for Valchor (nitrogen mustard 0.02% gel). The applicant's proposed indication 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)

The applicant has not provided all necessary non-clinical studies for review and will be relying on the literature and reference listed product for Valchor.

2. Background

The Applicant has submitted a 505b 2 application for Valchor, mechlorethamine, a nitrogen mustard. Mechlorethamine as a topical gel has been used without FDA approval for nearly 50 years to treat Mycosis Fungoides (MF) at concentrations ranging from 0.01% to 0.04%.

Currently topical nitrogen mustard applications are compounded at a compounding pharmacy.

Per the CMC review addendum the reference listed drug is: NDA#6695.

3. CMC/Device

Drs. Russell and Pope-Miksinski reviewed this supplement. They do not recommend approval. In their reviews they state the following in review #1:

A. Recommendation and Conclusion on Approvability

This is a recommendation to not approve this product from a Chemistry, Manufacturing and Controls standpoint. The clinical supplies for the single pivotal trial were not tested for impurities on release or stability, and were therefore insufficiently characterized. As a result, there are several outstanding deficiencies regarding comparability between clinical and commercial products, product specifications and expiry. Therefore the submitted information does not support a commercially viable product.

These, and additional deficiencies and comments, are listed below and at the end of this review and should be referenced in future review cycles.

The following language should be inserted in the Complete Response Action letter:

CMC Deficiencies:

1. Due to insufficient characterization, comparability between the clinical and commercial products has not been demonstrated.

2. At time of release, the proposed commercial drug product lots (UIP lots 094I1209B, 013I0210B and 017I0210B) were not sufficiently characterized.
3. Impurity levels in the commercial product cannot be qualified by clinical experience as proposed due to insufficient characterization of clinical and commercial lots on release and stability. Consequently, the proposed acceptance criteria for impurities in the proposed drug product specifications are not acceptable.
4. A product expiry cannot be established due to insufficient release data for the commercial lots of drug product and the lack of established acceptance criteria for the stability specifications.
5. Specify the supplier(s) of the starting material (b) (4) *in section S.2.3.*
6. Correct the discrepancy in Table (3.2.S.4) 2 of page 7, section 3.2.S.4. (b) (4)
7. Validation of the analytical method for assay/impurities submitted was for Method (b) (4)*, which is not the method identified in the drug product specifications. Provide validation for the assay/impurities method* (b) (4) *identified as the NDA method in the drug product specifications*
8. The validation report submitted for the analytical method for BHT (b) (4) *indicates that a placebo formulation (lot 04201009 trial 1) was used in place of product. Identify the test sample used in the submitted validation report. Provide validation of the method with product or demonstrate that the submitted validation conducted with placebo provides comparable results as product.*
9. Batch Analysis: Revise Table (3.2.P.5.4)2 titled "Batch Analyses of Drug Product – NDA Stability Lots – Manufactured at UIP; (b) (4) *Batch Size; 60g Tubes" to report only data collected at release* (b) (4) *and by the proposed specification methods submitted in Table 3 "Drug Product Specification – Release".*

Alternately, revise the table to include in the body of the table, for each data point:

- *date the test was conducted*
- *age of lot at test date, measured from date of lot manufacture*
- *storage conditions of the lot from manufacture to test date*
- *analysis method used, including method identification to correlate to submitted NDA methods listed in the specifications.*

Provide analytical procedures for analytical methods not already submitted and discuss correlation of results to those obtained by the NDA method. Explain the suitability of any data collected beyond release and using non-NDA methods for establishing the quality of the commercial product

10. Specifications: Impurity levels in the commercial product cannot be evaluated for qualification because a maximum daily dose has not been established. Establish a maximum daily dose.
11. Specifications: (b) (4) *acceptance criteria in the commercial product cannot be*

evaluated for release specification due to the absence of clinical and commercial lot release data. Further, the proposed level (b) (4) *in the stability specification is not supported by commercial lot manufacturing experience. Revise the proposed acceptance criteria* (b) (4) *in the drug product to reflect lot history.*
12. Stability specifications: The proposed specifications submitted for stability of the drug product do not include the test method. Revise the specifications to include attribute, method and acceptance criteria.
13. Expiry: (b) (4) *establish an in-use expiry period, based on study results, to begin at first dispense.*

CMC Comments:
The following additional issues were identified during this review cycle and are provided for your reference. While not comprehensive, consider these comments in your development of a complete and updated Module 3:
1. Provide a USAN name for the drug substance in section S.1.1.
2. Provide a CAS number for the starting material (b) (4) *in section S.2.3.*
3. In section 3.2.S.4, the proposed acceptance criterion for the individual related substances of drug substance specification is above the ICH qualification threshold. Tighten this acceptance criterion according to the ICH Q3A guidelines.
4. In section 3.2.S.4, the proposed acceptance criterion for the total related substances of the drug substance specification appears to be too wide based on your submitted batch history. Tighten this acceptance criterion to more accurately reflect your drug substance manufacturing capability.

4. Nonclinical Pharmacology/Toxicology

Dr Saber provided the following recommendation in her review:

The Applicant should either lower the specifications for the impurities in the drug product (b) (4) *as defined by ICH Q3B (R2) or adequately justify the proposed specifications.* (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

No issues were identified that would preclude approval.

From Dr. Lubin's review:

During the IND development of MF the Agency has recommended the collection of

plasma samples to measure MCH concentrations to confirm that there is no systemic exposure to the drug. Per the agreement with the FDA, blood samples were collected and analyzed in a subset of patients.

The MCH plasma concentrations were assayed in a cohort of patients in the phase 2/3 pivotal clinical trial 2005NMMF-201-US (n= 260), and both MCH and the half mustard (b) (4) *plasma concentrations were assayed in a cohort in trial 2007NMMF-202-US (n= 100). In both studies, there were no detectable concentrations of MCH or half mustard in any of the samples assayed, including those taken from patients who received whole body treatment.*

6. Clinical Microbiology

No issues were identified that would preclude approval.

7. Clinical/Statistical-Efficacy

From the Medical Officer's review of efficacy:

The efficacy of Valchlor was evaluated in 242 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key efficacy results from this non-inferiority clinical trial are listed below.

- *The primary endpoint was CAILS response (based on maximum of 5 index lesions per patient). Secondary endpoints include SWAT response (global response), duration of CAILS response, time to CAILS response, and time to CAILS progression. Non-inferiority to active control would be demonstrated if the lower limit of the 95% confidence interval of response rate ratio (Valchlor:control) is ≥ 0.75.*
- *Clinical trial 2005NMMF-201-US achieved its primary endpoint. The CAILS response rate ratio was 1.24 with 95%CI of 0.98 to 1.58. The CAILS response rate was 60% in Valchlor arm and 48% in control arm.*
- *Secondary endpoints supported the primary endpoint result.*
  – The SWAT response rate ratio was 1.07 with 95%CI of 0.82 to 1.39. The SWAT response rate was 50% in the Valchlor arm, and 46% in the control arm.
  – Time to CAILS response and time to SWAT response were similar between treatment arms. Median time to response (CAILS or SWAT) was 4 months for the Valchlor arm, and 3 months for the control arm.
  – Duration of CAILS response and duration of SWAT response were similar between treatment arms. Median duration of response (CAILS or SWAT) was not reached.
- *The trial population consisted of 242 patients enrolled from U.S. sites. Patients were required to have central and local pathology confirmation of the diagnosis of mycosis fungoides. All patients had at least one prior therapy. There was similar distribution of demographic parameters (gender, age, race) and*

baseline disease characteristics (stage of disease, duration of disease, prior therapies) between treatment arms.

However, due to inadequate product quality characterization of clinical trial lots of Valchlor (refer to Section 4.1), the above efficacy results cannot be extrapolated to the proposed commercial product lots of Valchlor. The applicant will need to conduct one or more clinical trials to establish the efficacy of commercial product lots of Valchlor.

From the Medical Officer's summary of the application:

The benefit-risk of Valchlor for the applicant's proposed indication cannot be adequately assessed. The primary basis of this NDA is clinical trial 2005NMMF-201-US (Study-201), a Phase 2, randomized, single-blinded, active-controlled clinical trial of topical mechlorethamine in patients with early stage mycosis fungoides.

Because the applicant did not collect impurity data on release and on stability of the drug product lots (b) (4) *used in the clinical trial, comparability cannot be established between the clinical trial drug product and proposed commercial drug product. Hence, the efficacy and safety data from Study-201 cannot be extrapolated to the proposed commercial drug product.*

Another deficiency identified with this application was the inadequate duration of followup for safety events post-treatment. The median duration of documented post-treatment follow-up for detection of secondary cutaneous malignancies (i.e., non-melanoma cutaneous skin cancer) was 1 day post-treatment cessation in both treatment arms.

Therefore, the efficacy and safety results of Study-201 cannot be used as the basis of approval for Valchlor. The applicant will need to conduct one or more clinical trials to demonstrate substantial evidence of efficacy and safety for the proposed commercial drug product. The design and results of Study-201 may be used to inform the design and conduct of such additional clinical trials.

From the Statistical review:
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.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of efficacy.

8. Safety

From the Medical Officer's review of safety:

The safety of Valchlor was evaluated in 255 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key safety results from this clinical trial are listed below.

- *Topical mechlorethamine was applied once daily. The duration of treatment was similar between treatment arms with a median of approximately 52 weeks. Fifty-five percent of patients required suspension of treatment or reduction of dose frequency during the clinical trial.*
- *Dermatitis is a known adverse event with topical mechlorethamine therapy. In this clinical trial, 73% in Valchlor arm and 69% in control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in Valchlor arm and 19% in control arm. Treatment discontinuations due to AEs (22% in Valchlor arm, 18% in control arm) were due to skin-related AEs. Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial.*
- *Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up. Eight patients developed nMSC during treatment with topical mechlorethamine. Risk factors associated with development of nMSC include age $\geq$ 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).*

However, due to inadequate product quality characterization of clinical trial lots of Valchlor (refer to Section 4.1), the above safety results cannot be extrapolated to the proposed commercial product lots of Valchlor. Applicant will need to conduct one or more clinical trials to establish the safety of commercial product lots of Valchlor.

In addition, post-treatment safety follow-up in Study-201 is inadequate in duration to assess the long-term safety risks, including risk of development of secondary skin cancers. The median duration of documented follow-up post-treatment was 1 day posttreatment cessation in both treatment arms. Per protocol, 12 months of follow-up was recommended for all patients following cessation of treatment for any reason.

I concur with the conclusions of the clinical and statistical review teams regarding the demonstration of safety.

9. Advisory Committee Meeting

This product was not discussed at an advisory committee meeting.

10. Pediatrics

N/A – orphan product

11. Other Relevant Regulatory Issues

The Office of Scientific Investigation did not uncover any reliability issues with regard to the clinical study conducted for the indication.

12. Labeling – N/A

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Complete Response due to lack of comparability between the clinical trial lots and the commercial lots. The letter will have 17 identified deficiencies involving CMC, pharm tox, and clinical. In addition, the letter will contain additional comments to improve the application if it is resubmitted.

- Risk Benefit Assessment
- Recommendation for Post marketing Risk Management Activities
- Recommendation for other Post marketing Study Requirements (PMR)/ Commitments (PMC)

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/s/

ANN T FARRELL
05/03/2012

Cross-Discipline Team Leader Review

Date	April 24, 2012
From	Albert Deisseroth, MD, PhD
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA/BLA # Supplement#	NDA 202317
Applicant	Ceptaris Therapeutics, Inc.
Date of Submission	July 27, 2011
PDUFA Goal Date	May 27, 2012
Name / Established (USAN) names	Valchlor
Dosage forms / Strength	0.02% gel
Applicant's Proposed Indication(s)	CTCL Stage I (b) (4) second line therapy
Recommended:	Complete Response

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	R. Angelo de Claro, MD
Statistical Review	Yun Wang, PhD/Mark Rothmann, PhD/Rajeshwari Sridhara,, PhD
Pharmacology Toxicology Review	Yosh Chopra, PhD/Haleh Saber, PhD
ONDQA-CMC and Biopharmaceutic Reviews	Anne Marie Russell, PhD/Gaeton Ladouceur, PhD/Janice Brown, PhD/Sarah Miksinski Pope, PhD/Richard Lostritto, PhD
Microbiology Review	Stephen Langille, PhD
Clinical Pharmacology Review	Rachelle Marie Lubin, PharmD/Julie Bullock, PharmD
OSI/DGCPC	Anthony Orencia, MD

1. Introduction

On July 27, 2011, Yaupon Therapeutics, Inc. (now re-named as Ceptaris Therapeutics, Inc.) submitted a 505(b)(2) NDA for its proprietary topical formulation (hereafter referred to as Valchlor) of mechlorethamine HCL (from this point on referred to as nitrogen mustard) in eCDT format for the following proposed indication: the topical treatment of (b) (4) Stage 1A, IB (b) (4) mycosis fungoides (MF) type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy (b) (4)

The NDA was supported by one randomized (stratified for Stage IA, IB or IIA) observer blinded phase II/III trial (Protocol 2005NMMF-201-US) which was designed to determine if the Ceptaris formulation (in a proprietary propylene glycol base) of 0.02% nitrogen mustard was non-inferior to a pharmacy-compounded formulation of 0.02% nitrogen mustard in an Aquaphor base in 260 patients with Stage I or IIA mycosis fungoides. All patients were treated daily (with the frequency of treatment adjusted for toxicity) in an outpatient setting for up to 12 months. This trial was conducted under an FDA Special Protocol Assessment (SPA).

The primary efficacy endpoint was the response rate as measured by the proportion of patients on each arm who experienced ≥50% improvement in the baseline Composite Assessment of Index Lesion Severity (CAILS) score. The key secondary endpoint was the response rate as measured by the proportion of patients on each arm who achieved ≥50% improvement in the Severity Weighted Assessment Tool (SWAT). Patients were supposed to be followed off study for an additional 12 months to assess participants for the development of non-melanoma skin cancers. The trial met both its primary and key secondary endpoints of non-inferiority.

Unfortunately, the benefit-risk of Valchlor cannot be assessed because Ceptaris did not collect impurity data on release and on stability (b) (4) of the drug product lots (b) (4) used in the clinical trial. Consequently, there is no comparability bridge from the GMP lots used for the clinical trial to the proposed commercial drug product. Therefore, the efficacy and safety data from Protocol 2005NMMF-201-US cannot be extrapolated to the proposed commercial drug product.

There were in addition many other deficiencies revealed by the FDA review including inadequate duration of follow-up for safety events post treatment (the median duration of follow-up for secondary cutaneous malignancies was 1 day post-treatment cessation in both arms), and a number of other CMC issues which will be reviewed in detail below.

CDTL Recommendation: The recommendation of the CDTL review is a Complete Response regulatory action.

2. Background

Topical application of nitrogen mustard for treatment of mycosis fungoides has been used in practice for over 40 years. In the beginning, an aqueous solution of nitrogen mustard was used for topical treatment. Although this formulation was capable of inducing responses of cutaneous disease, it was associated with a 60% incidence of allergic dermatitis which frequently resulted in the discontinuation of the treatment. This side effect eventually led to the development of a gel formulation of 0.02% nitrogen mustard in Aquaphor, which was prepared by compounding pharmacies. This formulation appeared to be equally effective with the aqueous formulation and was associated with a decreased incidence of allergic dermatitis which required the discontinuation of treatment. Despite the reduction in the incidence of allergic dermatitis, topical nitrogen mustard, even when formulated in Aquaphor, is associated with contact irritant dermatitis in a third of patients. This complication is managed with changes in schedule of the application of topical nitrogen mustard, and topical application of corticosteroids.

This community practice of off-label use of topical nitrogen mustard has led to a recommendation by the National Comprehensive Cancer Network (NCCN) for the use of topical nitrogen mustard therapy in the treatment of limited/localized as well as generalized skin involvement of MF. The extensive body of clinical experience and literature on the use of topical nitrogen mustard led to the acceptance by the practicing community of a concentration of between 0.01-0.02% of nitrogen mustard in Aquaphor.

Although the non-inferiority clinical trial 2005NMMF-201-US, in which the response rate of the Ceptaris topical formulation was compared to the Aquaphor formulation, was carried out by Ceptaris Therapeutics, Inc. under an FDA SPA agreement, other parts of the drug development program were less well developed.

The FDA held eight meetings with representatives of Ceptaris from 2004 to 2010. Six of these meetings included representatives of the FDA CMC review division. As shown below by Table 1, which was prepared by Dr. Ann Marie Russell, ONDQA-CMC of the FDA, representatives of the FDA CMC review division repeatedly (in 2004, 2006, and 2010) advised Ceptaris to characterize the impurities in the drug product clinical lots on release and stability. As is also outlined in Table 1 below, representatives of Ceptaris repeatedly agreed to do so and then did not measure the impurity levels in the lots of drug product used in the pivotal clinical trial.

Because the applicant did not collect the requested impurity data on release and on stability (b) (4) of the drug product lots used in the clinical trial, (b) (4) comparability cannot be established between the clinical trial drug product used in study 2005NMMF-201-US and the proposed commercial drug product. Hence, the efficacy and safety data from Study 2005NMMF-201-US, the pivotal non-inferiority trial on which NDA202317 is based, cannot be applied to the proposed commercial drug product.

Table 1 below lists meetings held between the FDA and Ceparis in chronological order, a summary of the FDA CMC advice provided regarding drug product characterization in the meeting, and Ceptaris' commitment and action by the time of NDA submission. Note that emphasis is on the drug product impurity issue used during Study 2005NMMF-201-US, and that the table does not include a comprehensive listing of all CMC issues addressed during development.

Table 1: Meetings Held Between FDA and Ceptaris from 2004 to 2010

Type and date of meeting	Summary of FDA drug product advice provided at meeting	Ceptaris response at meeting	Subsequent action by Ceptaris on CMC issue
1. Pre-IND (July, 2004)	Validate the assay method per guidance	Agreed	Validated the assay
IND Safety Comments (November, 2004)	Provide drug substance and drug product information – including drug product stability data.	"We will provide the suggested information during the clinical trial"	Provided some of the requested information but no stability data on impurity levels as advised.
2. Meeting (May, 2005)	Mostly clinical – one minor CMC issue regarding supply of excipient	----------	----------
3. Meeting (December, 2005)	Provide stability data prior to initiating pivotal study.	Agreed	Provided in April 2006 meeting package (inadequate)
4. CMC-only (April, 2006)	Many CMC issues were discussed including advice to "identify and characterize degradation products per ICHQ3B by the end of Phase 2 studies."	Agreed	Did not identify or characterize the degradation products in lots of drug product used in the pivotal clinical trial.
5. Meeting (July, 2008)	Statistics only	----------	----------
6. Pre-NDA (March, 2010)	Non-clinical only	----------	----------
7. Pre-NDA CMC-only (March 2010)	Many CMC issues, including advice to report impurities in the drug product.	Agreed	Did not report impurities in the clinical batches of drug product.
8. Pre-NDA (December, 2010)	Mostly clinical and non-clinical issues were discussed including minor CMC issues.	----------	----------

This failure of Ceptaris to collect the requested impurity data on release and on stability (b) (4) of the drug product lots used in the clinical trial creates a situation in which a Complete Response regulatory action is being recommended despite the fact that the pivotal trial of the NDA met its efficacy and safety endpoints. This is because the results of study 2005NMMF-201-US cannot be extrapolated to the drug product which is being proposed for post approval marketing. The recommendation of the FDA to Ceptaris

Therapeutics, Inc. for going forward is to conduct one or more clinical trials using the proposed commercial drug product to generate substantial evidence of efficacy and safety of the proposed commercial drug product. The design and results of study 2005NMMF-201-US can be used to inform the design and conduct such additional studies.

3. CMC

The following represents an executive summary of the review findings of the CMC Review Team. As outlined above in Table 1, the CMC review division repeatedly (in 2004, 2006, and 2010) advised Ceptaris to characterize drug product clinical lots on release and stability. As is also outlined in Table 1, representatives of Ceptaris repeatedly agreed to do so and then did not measure the impurity levels in the lots of drug product used in the pivotal clinical trial. Outlined below is a list of additional but related issues identified by the CMC review which have not been satisfactorily answered by Ceptaris.

Questions Unanswered During the CMC Review of the Drug Development Program

1. It is not clear how the clinical data submitted is able to justify the specifications proposed for impurities in the drug product. The impurity data analysis submitted in Table (3.2.P.5.6.8)2 of the NDA entitled "Summary of Ranges of Impurities in Yaupon (Ceptaris) Formulation and Associated ICH Identification and Qualification Thresholds" was performed on data collected on lots which were not used in clinical or non-clinical studies. Further, the referenced 3 UIP stability lots (produced for the commercial drug product by the University of Iowa Pharmaceuticals, Inc. (UIP) cited in Table 3.2.P.5.6.8 were manufactured at a different site, by a different manufacturer, by a different process, at a different scale and packaged into a different size tube than the majority of the clinical lots used for study 2005NMMF-201-US. (b) (4) Ceptaris never addressed these issues to the satisfaction of the FDA CMC division.

2. The FDA asked Ceptaris to provide release and stability impurity batch data for all clinical lots and to describe the storage conditions from time of release until testing for each lot listed in Table 3.2.P.2.3.3 entitled "(b) (4) and UIP lots tested using the proposed NDA Methods". Ceptaris was asked to provide convincing scientific justification for relating the impurity levels of these lots to support its proposed comparability studies (b) (4) The FDA stated that this justification should include discussion of changes to storage temperature, stability, differences in manufacturing site, process, scale and differences in tube size. Ceptaris did not provide responses that satisfactorily addressed the concerns of the CMC reviewers.

Specific Deficiencies Noted by the CMC Review:

1. Due to insufficient characterization, comparability between the clinical and commercial products has not been demonstrated.

2. At time of release, the proposed commercial drug product lots (UIP lots 094I1209B, 013I0210B and 017I0210B) were not sufficiently characterized.

3. Impurity levels in the commercial product cannot be qualified by clinical experience as proposed due to insufficient characterization of clinical and commercial lots on release and stability. Consequently, the proposed acceptance criteria for impurities in the proposed drug product specifications are not acceptable.

4. A product expiry cannot be established due to insufficient release data for the commercial lots of drug product and the lack of established acceptance criteria for the stability specifications.

5. The Applicant did not specify the supplier(s) of the starting material (b) (4) in section S.2.3.

6. There is a discrepancy in Table (3.2.S.4) 2 of page 7, section 3.2.S.4. (b) (4)

7. Validation of the analytical method for assay/impurities submitted was for Method (b) (4) which is not the method identified in the drug product specifications. Provide validation for the assay/impurities method (b) (4) identified as the NDA method in the drug product specifications

8. The validation report submitted for the analytical method for BHT (b) (4) indicates that a placebo formulation (lot 04201009 trial 1) was used in place of product. Identify the test sample used in the submitted validation report. Provide validation of the method with product or demonstrate that the submitted validation conducted with placebo provides comparable results as product.

9. Batch Analysis: The Applicant should revise Table (3.2.P.5.4)2 titled "Batch Analyses of Drug Product – NDA Stability Lots – Manufactured at UIP; (b) (4) Batch Size; 60g Tubes" to report only data collected at release (b) (4) and by the proposed specification methods submitted in Table 3 "Drug Product Specification – Release".

Alternately, the Applicant should revise the table to include in the body of the table, for each data point:

a. the date the test was conducted
b. the age of lot at test date, measured from date of lot manufacture
c. the storage conditions of the lot from manufacture to test date

d. the analysis method used, including method identification to correlate to submitted NDA methods listed in the specifications.

The Applicant should provide analytical procedures for analytical methods not already submitted and discuss correlation of results to those obtained by the NDA method.

The Applicant should explain the suitability of any data collected beyond release and using non-NDA methods for establishing the quality of the commercial product.

10. Specifications: Impurity levels in the commercial product cannot be evaluated for qualification because a maximum daily dose has not been established. Establish a maximum daily dose.

11. Specifications: (b) (4) acceptance criteria in the commercial product cannot be evaluated for release specification due to the absence of clinical and commercial lot release data. Further, the proposed level (b) (4) in the stability specification is not supported by commercial lot manufacturing experience. Revise the proposed acceptance criteria (b) (4) in the drug product to reflect lot history.

12. Stability specifications: The proposed specifications submitted for stability of the drug product do not include the test method. Revise the specifications to include attribute, method and acceptance criteria.

13. Expiry: (b) (4) establish an in-use expiry period, based on study results, to begin at first dispense.

Summary of the CMC Concerns and Regulatory Recommendation of the CMC Review Team: Ceptaris has failed to characterize the impurities of the clinical production lots that were used for the pivotal trial 2005NMMF-201-US, and failed to address the concerns raised by the CMC review division. Because these deficiencies of Ceptaris have led to the requirements of 21 CFER 314.50(d)(1) not being adequately met by the Applicant, a Complete Response regulatory action is recommended.

4. Nonclinical Pharmacology/Toxicology

The following is an executive summary of the review issues identified by the Nonclinical Pharmacology/Toxicology Review Team. (b) (4)

(b) (4)

Table 2: Impurities

(b) (4)

Recommendation of Pharmacology/Toxicology: The Applicant should either lower the specifications for the impurities in the drug product (b) (4) as defined by ICH Q3B (R2) or adequately justify the proposed specifications. (b) (4)

[redacted] (b) (4)

Due to these deficiencies, the labeling review has not been initiated. It is expected that most nonclinical information provided in the label for MUSTARGEN could be used to label VALCHLOR. The Applicant has also submitted published articles in support of the nonclinical sections of the label. The articles have not been reviewed at this time.

5. Clinical Pharmacology

The following is the executive summary of the review findings of the Clinical Pharmacology/Biopharmaceutics Review Team. Mechlorethamine, also known as nitrogen mustard, is an antineoplastic agent that has been previously approved for parenteral administration (marketed under the trade name Mustargen® NDA#6695), is used for the palliative treatment of Hodgkin's disease (Stages III and IV) and other cancers. The Applicant has developed a topical formulation of nitrogen mustard for the treatment of early stage (Stage IA, IB [redacted] (b) (4)) MF. Nitrogen mustard has been used without FDA approval for nearly 50 years as a topical treatment to MF at concentrations ranging from 0.01% to 0.04%.

During the IND development of MF, the Agency has recommended the collection of plasma samples to measure nitrogen mustard concentrations to confirm that there is no systemic exposure to the drug. Per the agreement with the FDA, blood samples were collected and analyzed in a subset of patients. The nitrogen mustard plasma concentrations were assayed in a cohort of patients in the phase 2/3 pivotal clinical trial 2005NMMF-201-US (n= 260), and both nitrogen mustard and the half mustard [redacted] (b) (4) plasma concentrations were assayed in a cohort in trial 2007NMMF-202-US (n= 100). In both studies, there were no detectable concentrations of nitrogen mustard or half mustard in any of the samples assayed, including those taken from patients who received whole body treatment.

Regulatory Recommendation of the Clinical Pharmacology/Biopharmaceutics Review Division: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 202317. The Clinical Pharmacology information submitted in NDA 202317 is acceptable from a Clinical Pharmacology perspective to support the approval of Valchlor (MCH HCL) 0.02% Gel.

6. Clinical Microbiology

The following sections represent an executive summary of the review issues identified by the Clinical Microbiology Review Team.

6.A. Brief Description of the Manufacturing Processes That Relate to Product Quality Microbiology: The drug product is formulated into a (b) (4) gel containing (b) (4) isopropanol. The drug product is manufactured under GMP conditions and is unlikely to support microbial growth.

Drug Product Composition: The drug product is a translucent gel for topical administration packaged in a multiple dose re-sealable (b) (4) tube. The drug product composition was provided in Table 3.2.P.1.2 of the application and is reproduced in Table 3 below.

The drug product consists of a number of organic components (b) (4) The risk of microbial proliferation in this product is minimal. However, the applicant (b) (4) has agreed to conduct microbial limits testing at release and on stability batches. Additional (b) (4) testing is not required based upon the chemical composition of the drug product.

Description of container closure system: The drug product is supplied in multiple dose (b) (4) tubes (b) (4)

(b) (4) The results of (b) (4) testing were provided in Report STL10-156 and Tables (3.2.P.2.5)1 and (3.2.P.2.5)2. Testing was conducted according (b) (4) methodology and the results of the testing conducted on three batches each of the (b) (4) tubes and the 60 g tubes. Each of the lots passed (b) (4) testing (b) (4)

6.B. Brief Description of Microbiology Deficiencies: No product quality microbiology deficiencies were identified based upon the information provided.

Table 3: Drug Product Composition

Component	Quality Standard	Function[1]	Percentage (% w/w)	Amount (g/tube)
Mechlorethamine Hydrochloride (MCH, NM)	USP	Active Pharmaceutical Ingredient	0.02	0.012
Diethylene Glycol Monoethyl Ether (diEGEE; (b) (4))[2]	NF	(b) (4)		
Propylene Glycol (PG)	USP			
Isopropyl Alcohol[2] (IPA)	USP			
Glycerin	USP			
Lactic Acid, (b) (4) (LA)	USP			
Hydroxypropylcellulose, (HPC (b) (4) (b) (4))	NF			
Sodium Chloride (NaCl)	USP			
(b) (4) Menthol	USP			
Edetate Disodium (b) (4) (b) (4)	USP			
Butylated Hydroxytoluene (BHT)	NF			
TOTAL			**100%**	**60g**

[1]Kibbe, AH, editor. Handbook of Pharmaceutical Excipients. 3rd ed. London: Pharmaceutical Press; 2000.

(b) (4)

6.C. Recommendation of Clinical Pharmacology: NDA 202317 is recommended for approval from the standpoint of product quality microbiology. No phase 4 commitments and/or agreements are recommended.

Regulatory Recommendation of the Clinical Pharmacology/Biopharmaceutics Review Division: The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 202317. The Clinical Pharmacology information submitted in NDA 202317 is acceptable from a Clinical Pharmacology perspective to support the approval of Valchlor (MCH HCL) 0.02% Gel.

7. Clinical/Statistical- Efficacy

The following is an executive summary of the review issues identified by the Clinical/Statistical-Efficacy Review Team. Topical nitrogen mustard has been evaluated for the management of MF for over 5 decades. Topical nitrogen mustard at a

concentration of 0.01 – 0.02% is recognizerd in community practice as an 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 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 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 Study 2005NMMF-201-US 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 involving the New York University Trial Site (NYU) described in the clinical study report of the Applicant's submission and this statistical review. The randomization issue did not impact the conclusion of non-inferiority on overall response rate. However, there are product issues for this application on whether the product used in this study can be linked to the marketed product. These latter issues may preclude an approval.

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Statistical Methodologies: Using the likelihood based methods of Miettinen and Nurminen, an estimate of ratio of CAILS response rates along with its 95% confidence limit was calculated for the ITT population excluding data from the NYU clinical trial site. 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.

Statistical and Clinical Reviewers' Conclusions:

a. 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.

b. The SWAT analysis results were consistent with CAILS results in supporting non-inferiority of PG formulation to AP formulation.

c. 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.

8. Safety

The following is an executive summary of the findings of the Safety Review Team. The safety of Valchlor was evaluated in 255 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key safety results from this clinical trial are listed below.

- Topical nitrogen mustard was applied once daily. The duration of treatment was similar between treatment arms with a median of approximately 52 weeks. Fifty-five percent of patients required suspension of treatment or reduction of dose frequency during the clinical trial.

- Dermatitis is a known adverse event with topical nitrogen mustard therapy. In this clinical trial, 73% in the Valchlor arm and 69% in the control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in the Valchlor arm and 19% in the control arm. Treatment discontinuations due to adverse events (22% in Valchlor arm, 18% in control arm) were due to skin-related adverse events. Most cases of dermatitis resolved, however 9% in the Valchlor arm and 13% in the control arm had residual dermatitis at the end of the clinical trial.

- Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up. Eight patients developed nMSC during treatment with topical nitrogen mustard. Risk factors associated with the development of nMSC include age ≥ 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).

However, due to inadequate product quality characterization of clinical trial lots of Valchlor (see above), the above safety results cannot be extrapolated to the proposed commercial product lots of Valchlor. The Applicant will need to conduct one or more clinical trials to establish the safety of commercial product lots of Valchlor.

In addition, post-treatment safety follow-up in Study-2005NMMF-201-US is inadequate in duration to assess the long-term safety risks, including risk of development of secondary skin cancers. The median duration of documented follow-up post-treatment was 1 day post-treatment cessation in both treatment arms. Per protocol, 12 months of follow-up was recommended for all patients following cessation of treatment for any reason.

9. Advisory Committee Meeting

No Advisory Committee meeting is scheduled.

10. Pediatrics

There is no pediatric indication which corresponds to MF. Due to inadequate product quality characterization of clinical trial lots of Valchlor, a Complete Response Regulatory Action will be issued for this NDA. Therefore, the pediatric issues are not being pursued.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No Issues
- **Exclusivity or Patent Issues of Concern:** None
- **Financial Disclosures**: Adequate and complete.
- **Other GCP Issues**: None
- **Office of Scientific Investigation (OSI) Audits: The following is an executive summary of the findings arising from DSI visits to the following sites:**

1. Madeleine Duvic, M.D. /Study Protocol 2005NMMF-201-US/Site #002 at Houston, TX. A total of 65 subjects were screened, 61 subjects were randomized and completed the study. An audit of 18 randomized subjects' records was conducted. The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms (CRFs), study drug accountability logs, study monitoring visits and correspondence. Informed consent documents and Applicant generated correspondence were also inspected.

2. Matthew B. Zook, M.D., Ph.D./Study Protocol 2005NMMF-201-US/Site #002 at Rockledge, PA. A total of 28 subjects were screened, 15 subjects were randomized, and 11 subjects completed the study. An audit of 15 randomized subjects' records was conducted.

3. Bruce Strober, M.D., Ph.D./ Study Protocol 2005NMMF-201-US/Site #007 at New York, NY (Previous address during conduct of this study); Farmington, CT (present address). A total of 24 subjects were screened, 18 were randomized and 6 subjects

completed the study. [Note: 4 subjects were voluntarily withdrawn, 4 subjects were withdrawn]

OSI Medical Officer Comments: Per OSI consult and discussions with the Division of Hematology Products (DHP), there was an Applicant-acknowledged incorrect randomization of 16 patients at the New York University (NYU) Site. The study coordinator at this clinical investigation site (Site #007) did not follow the randomization code. DHP wanted to verify the accuracy of the Applicant's assessment during the clinical audit. This error in randomization was acknowledged in the NDA submission to the Agency in Section 10.2 Protocol Deviations of the Clinical Study Report. This was also discussed during the Applicant's orientation face-to-face meeting with DHP on October 6, 2011. As acknowledged by the Applicant and submitted in its NDA, this problem occurred exclusively at Site #007 and not systematically throughout the study. DHP has clarified that the inclusion or omission of these 16 subjects (of 18 enrolled) at the NYU Site #007 in the analyses did not have any measurable impact on the conclusions reached about efficacy.

The above finding was corroborated during two Office of Regulatory Affairs (ORA) field visits: (a) January 17-20, 2012 with the senior clinical research coordinator for Study Protocol 2005NMMF-201-US at Site #007 and (b) February 22, 2012, with Dr. Bruce Strober, the original principal investigator for this study (b) (4) Reference ID: 3106796, Page -6 NDA 202317 nitrogen mustard (b) (4) Clinical Inspection Summary. Per ORA field staff, the original study research nurse, who was the only study-unblinded member of this clinical trial investigation, did not follow proper procedures for randomization.

The study-unblinded research nurse was involved in randomizing and dispensing of the test article. This original study research nurse assigned the PG formulation to all patients in stratum one with Stage 1A disease and AP formulation to all patients in stratum two with Stage 1B and IIA disease. This was discovered by another study-unblinded clinical research coordinator, who took over research responsibilities from the original research nurse, and reported the error to the originally study-blinded clinical site principal investigator, who then informed the Applicant. As part of the clinical site's preventive action plan per ORA, the Applicant was notified and the NYU Dermatopharmacology Unit of the Department of Dermatology transferred all drug dispensation responsibilities to the NYU investigative pharmacy. In summary, ORA confirmed that the error in randomization, noted by the Applicant in their NDA submission and during the ORA clinical audit with Dr. Strober, was an isolated incident at Site #007 with respect to Study Protocol 2005NMMF-201-US.

OSI Overall Assessment of Findings and Recommendations

Three clinical investigator sites were inspected in support of this application for Study Protocol 2005NMMF-201-US. No regulatory violations were noted or issued. Based upon review of inspectional findings for these clinical investigators, the study data collected appear generally reliable in support of the requested indication. OSI defers to

DHP regarding the decision to include or exclude these known, incorrectly randomized patients, as identified in the NDA submission, in their final analyses and deliberations.

- **Other discipline consults:** None

- **Any other outstanding regulatory issues:** None

12. Labeling

DMEPA concluded that the labels and labeling proposed by Ceptaris are unacceptable and introduce vulnerability that can lead to medication errors. These deficiencies have been communicated to the Applicant. Because of the decision of the FDA to issue a complete response for this NDA due to CMC issues, the issue of labeling was not pursued.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Complete Response

- Risk Benefit Assessment

The non-inferiority trial met its endpoints. There were no major safety issues. Thus, approval would have been granted had it not been for the failure on the part of Ceptaris to adequately characterize the impurities and stability of the clinical production lots used for the pivotal trial. Due to this failure, it is impossible to extrapolate the results of the pivotal trial to a post approval setting in which different lots of drug product will be utilized.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  None

- Recommended Comments to Applicant

  The Applicant will have to conduct one or more clinical trials to establish the efficacy and safety of the proposed commercial product.

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/s/

ALBERT B DEISSEROTH
04/24/2012

CLINICAL REVIEW

Application Type	NDA 505(b)(2) Efficacy Supplement
Application Number	202317
Priority or Standard	Standard
Submit Date	27 July 2011
Received Date	27 July 2011
PDUFA Goal Date	27 May 2012
Division / Office	DHP / OHOP
Reviewer Name	R. Angelo de Claro, M.D.
Review Completion Date	28 March 2012
Established Name	Mechlorethamine hydrochloride
Trade Name	Valchlor
Therapeutic Class	Antineoplastic
Applicant	Yaupon Therapeutics, Inc., changed to Ceptaris Therapeutics, Inc. (5 Jan 2012)
Formulation	0.02% gel
Dosing Regimen	Topical, once daily
Indication	CTCL Stage I (b) (4) second-line therapy
Intended Population	Adults > 18 years

Template Version: March 6, 2009

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Table of Abbreviations

AE	Adverse Event
AP	Aquaphor (control arm formulation base)
BCC	Basal Cell Carcinoma
BSA	Body Surface Area
CAILS	Composite Assessment of Index Lesion Severity
	(b) (4)
CR	Complete Response
CRF	Case Report Form
CRO	Clinical Research Organization
CTCL	Cutaneous T-Cell Lymphoma
IQR	Interquartile Range
ITT	Intent-to-Treat
MCH	Mechlorethamine Hydrochloride
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis Fungoides
NE	Not Estimable
NM	Nitrogen Mustard (mechlorethamine)
nMSC	Non-Melanoma Skin Cancer
PD	Progressive Disease
PG	Propylene Glycol (Yaupon formulation base)
PR	Partial Response
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SD	Stable Disease, Standard Deviation
SOC	System Organ Class
SWAT	Severity Weighted Assessment Tool
TLT	Treatment Limiting Toxicity
UIP	University of Iowa Pharmaceuticals

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a complete response for this 505(b)(2) application (NDA 202317).

1.2 Risk Benefit Assessment

The benefit-risk of Valchlor for the applicant's proposed indication cannot be adequately assessed. The primary basis of this NDA is clinical trial 2005NMMF-201-US (Study-201), a Phase 2, randomized, single-blinded, active-controlled clinical trial of topical mechlorethamine in patients with early stage mycosis fungoides.

Because the applicant did not collect impurity data on release and on stability (b) (4) of the drug product lots (b) (4) used in the clinical trial, comparability cannot be established between the clinical trial drug product and proposed commercial drug product. Hence, the efficacy and safety data from Study-201 cannot be extrapolated to the proposed commercial drug product.

Another deficiency identified with this application was the inadequate duration of follow-up for safety events post-treatment. The median duration of documented post-treatment follow-up for detection of secondary cutaneous malignancies (i.e., non-melanoma cutaneous skin cancer) was 1 day post-treatment cessation in both treatment arms.

Therefore, the efficacy and safety results of Study-201 cannot be used as the basis of approval for Valchlor. The applicant will need to conduct one or more clinical trials to demonstrate substantial evidence of efficacy and safety for the proposed commercial drug product. The design and results of Study-201 may be used to inform the design and conduct of such additional clinical trials.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The applicant submitted a REMS assessment plan consisting of a medication guide (b) (4) The applicant's REMS assessment plan could not be evaluated due to complete response issues identified with the application.

1.4 Recommendations for Postmarket Requirements and Commitments

Evaluation for postmarket requirements and commitments could not be done due to complete response issues identified with the application.

2 Introduction and Regulatory Background

Cutaneous T-Cell Lymphomas (CTCL) are a heterogeneous group of lymphoproliferative diseases characterized by infiltration of the skin by malignant T-cells. They comprise approximately 4% of non-Hodgkin's lymphomas in the United States. Mycosis fungoides (MF) is the most common presentation (54%). The Surveillance, Epidemiology, and End Results Program (SEER), tracing registries in the United States from 1973 through 2007 reported an incidence of 4.1 cases of MF per million per year (SEER 1973-2007).

MF, first described in 1835, commonly begins with a nonspecific scaly eruption that leads to the development of patches/plaques. With further progress, the disease advances with the formation of tumors, generalized erythroderma often with a leukemic phase (Sezary syndrome) and lymphadenopathy. Eventually, wide-spread visceral involvement may lead to death from the disease. Ulceration of tumors, with secondary infection is also a common cause of morbidity and death.

The diagnosis is made with skin biopsy, with the demonstration of a band-like infiltrate of lymphocytes infiltrating the papillary dermis. The cellular composition consists of small, medium-sized and sometimes large mononuclear cells with hyperchromatic, cerebriform nuclei. The malignant cells may cluster with a perinuclear halo, the so-called Pautrier's microabscess. The diagnosis is further confirmed with immunophenotyping and DNA analysis of the T-cell-receptor gene rearrangement to define the clonal population.

Clinical staging serves to distinguish prognostic groups. Good-risk patients, who have plaque-only disease without lymph node, blood or visceral involvement, have an estimated median survival of more than 12 years. Intermediate-risk patients, with tumors, erythroderma or plaque disease with lymph node or blood involvement, but no visceral involvement, have a median survival of approximately 5 years, whereas poor-risk patients, with visceral involvement, have a median survival of approximately 2.5 years. Based from the experience at Stanford University, the survival outcome of patients with clinical Stage IA MF (limited patch/plaque <10% BSA, without clinically involved lymph nodes), was not altered compared to a matched control population.

Topical nitrogen mustard (mechlorethamine) has been evaluated for the management of MF since the 1950s, predominantly through retrospective analysis of medical records. Prior to the clinical trial in the application, there have been no randomized clinical trials with nitrogen mustard for the management of MF.

Reviewer Comment: The terms "nitrogen mustard" and "mechlorethamine" are used interchangeably in this review.

The major toxicity of topical nitrogen mustard is allergic contact dermatitis, which occurs in 35-70% of patients and often results in discontinuation of therapy.

For this 505(b)(2) New Drug Application for marketing authorization of the Applicant's proprietary formulation containing mechlorethamine hydrochloride, Mustargen® will be used as the Reference Listed Drug (RLD). The Applicant is proposing to accept sections of the current labeling language for Mustargen® including Warnings for the Use of the Product (modified for the Yaupon topical product), Carcinogenesis, Mutagenesis, Impairment of Fertility, Usage in Pregnancy, and Pregnancy Category.

2.1 Product Information

Established Name: Mechlorethamine hydrochloride
Proprietary Name: VALCHLOR

Applicant: Yaupon Therapeutics, Inc.
(changed to Ceptaris Therapeutics, Inc. on 5 January 2012)
101 Linderwood Drive Suite 400
Malvern, PA 19355

Drug Class: Antineoplastic

Applicant's Proposed Indication: VALCHLOR 0.02% is an antineoplastic agent indicated 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)

Applicant's Proposed Dosage and Administration: VALCHLOR 0.02% is to be applied daily on completely dry skin (at least 4 hours before or 30 minutes after showering)

Reviewer Comment: Throughout this review, the Applicant is referred to as Yaupon or Yaupon Therapeutics, Inc. The name change of the Applicant occurred during the review cycle, when majority of this clinical review had already been drafted.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several FDA approved drugs for the treatment of CTCL (refer to Table 1). Not shown in the table, methotrexate, methoxsalen, vinblastine, and cyclophosphamide are also approved for the treatment of CTCL. Note that mechlorethamine is approved for the treatment of mycosis fungoides through an intravenous route of administration.

Table 1 Recent FDA Approvals for CTCL

Drug (Approval)	Indication	Basis for Approval
Targretin (Regular, 2000)	For the topical treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies	Two single arm trials Trial 1 (N=50): ORR 26%, CR 2% Trial 2 (N=67): not evaluable for efficacy (dose-seeking design)
Ontak (AA, 1999) (Regular, 2008)	For the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor	AA: RCT, DB (N=71) ORR 30% Regular: RCT, DB, placebo-control (N=144) ORR 46%, PFS HR 0.27
Zolinza (Regular, 2006)	For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.	One single arm trial (N=74) ORR 30%
Istodax (Regular, 2009)	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy	Two single arm trials Trial 1 (N=96): ORR 34% Trial 2 (N=71): ORR 35%

Other skin-directed therapies for MF (from 2011 NCCN guidelines) include: topical corticosteroids, topical chemotherapy (nitrogen mustard, carmustine), radiation therapy (local, total skin electron beam), topical retinoids, phototherapy, topical imiquimod.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, mechlorethamine, is approved in the United States for intravenous and intracavitary (intrapleural, intraperitoneal, or intrapericardial) use. Mustargen (mechlorethamine HCl) is supplied in the United States as 100 mg vials for the aforementioned use.

2.4 Important Safety Issues With Consideration to Related Drugs

Mechlorethamine is an antineoplastic alkylating agent. Known class effects of intravenous alkylating agents include myelosuppression, nausea, vomiting, hypersensitivity reactions, infertility, and secondary malignancies. In addition, mechlorethamine is also an irritant and may cause thrombophlebitis. Extravasation of mechlorethamine into subcutaneous tissues result in painful inflammation. The Mustargen label recommends avoidance of contact with mucosal membranes, especially those of the eyes.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held on 30 July 2004. Yaupon Therapeutics, Inc. opened the IND on 7 October 2004. FDA granted Orphan Drug designation on 17 August 2004 and Fast Track designation on 31 May 2006. Clinical trial 2005NMMF-201-US was discussed with the FDA, and was eventually granted Special Protocol Assessment. Pre-NDA meeting was held on 21 December 2010. NDA 202317 was received 27 July 2011, and was filed for standard review on 26 September 2011.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA was submitted using eNDA/CTD Hybrid format. The applicant's waiver request for non-eCTD electronic submission was granted on 29 October 2010.

The submission contains all of the required components of the Common Technical Document (CTD). The overall quality and integrity of the electronic hybrid submission is acceptable.

3.2 Compliance with Good Clinical Practices

Protocol 2005NMMF-201-US and its amendments have been reviewed and approved by each investigator's Institutional Review Board (IRB). The study was conducted according to applicable State and Federal regulations and ICH Good Clinical Practice (GCP) guidelines. The proposed informed consent form, which was compliant with regulatory requirements, was reviewed and approved by the IRB at each site prior to initiation of the study. These requirements are in accordance with the Code of Federal Regulations as detailed in 21 CFR §50.25 and the Declaration of Helsinki.

Clinical site inspections were requested for three sites MD Anderson Cancer Center (MDACC), Fox Chase Cancer Center (FCCC), and New York University. FDA Office of Scientific Investigations (OSI) overall assessment of these three sites was "the study data collected appear generally reliable in support of the requested indication."

Specifically, regarding the protocol violation with randomization that involved New York University, OSI noted that the error in randomization, disclosed by the Applicant in the NDA submission and during the clinical audit, was an isolated incident with respect to Study Protocol 2005NMMF-201-US. As part of the clinical site's preventive action plan per ORA, the Applicant was notified and the NYU Dermatopharmacology Unit of the Department of Dermatology transferred all dispensation responsibilities to the NYU investigative pharmacy.

3.3 Financial Disclosures

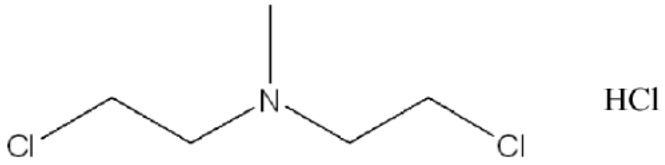
In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirements and certification.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The structure of mechlorethamine hydrochloride is shown in Figure 1. Refer to CMC review for further details.

Figure 1 Structure of Mechlorethamine Hydrochloride



Molecular Formula:	$C_5H_{11}Cl_2N \cdot HCl$
Molecular Weight:	192.51

The initial clinical trial material was manufactured (b) (4) To prepare for commercial scale operations, the drug product manufacturing process was transferred to the University of Iowa Pharmaceuticals (UIP) and scaled-up. The proposed commercial drug product manufacturing site is UIP.

Drug product (MCH gel 0.02% w/w) manufactured at both (b) (4) and UIP was used in Study 201. The (b) (4) drug product lots used in Study 201 were manufactured (b) (4) and a clinical lot was made at the University of Iowa Pharmaceuticals (UIP) (b) (4)

Clinical Reviewer Comment: The review team (DHP clinical, DHOT, CMC) had two separate teleconferences with the Applicant on December 8, 2011 and December 16, 2011 to discuss the CMC deficiencies with regards to lack of collection of impurity data for the (b) (4) clinical lots.

The CMC review team noted that impurity data was not collected at release and on stability for the (b) (4) clinical lots. The applicant acknowledged this finding in response

sent with amendment 14 (received on 23 December 2011): "Impurity data was not collected at release and on stability for the lots [redacted]"

Therefore, comparability between [redacted] and UIP drug products cannot be established. Considering that [redacted] the exposure in patients treated with Valchlor were from [redacted] product, the lack of adequate characterization of [redacted] drug product affects the interpretability of clinical trial results from Study 201.

The applicant submitted additional safety analysis with amendment 17 (received on 17 January 2012). The applicant claims that clinical data in Study-201 is helpful in comparing the [redacted] and UIP products in the Valchlor treatment arm. Fourteen patients received treatment with UIP product during the conduct of Study-201.

Clinical Reviewer Comment: Clinical data in Study-201 is not evaluable to compare the efficacy and safety between the [redacted] and UIP drug products.

There were only 14 of 130 patients in the Valchlor treatment arm who received UIP during the course of the trial. All of these 14 patients had already received treatment with [redacted] product prior to start of treatment with UIP product (refer to Table 2). The median duration of treatment was 256 days (range 168 to 329 days) on [redacted] product prior to transition to UIP product. Any clinical data generated during the period of UIP treatment is confounded by the prior [redacted] treatment in all of these 14 patients.

Table 2 Exposure to [redacted] and UIP Drug Products in Patients on the Valchlor Treatment Arm in Study-201

USUBJID	Days on [redacted] treatment prior to transition to UIP	Days on UIP treatment	Percentage of total treatment duration with UIP
2005NMMF-201-US-002-0059	259	107	29%
2005NMMF-201-US-002-0076	328	34	9%
2005NMMF-201-US-002-0079	168	128	43%
2005NMMF-201-US-002-0081	252	96	28%
2005NMMF-201-US-005-0025	245	126	34%
2005NMMF-201-US-009-0009	294	70	19%
2005NMMF-201-US-010-0044	309	63	17%
2005NMMF-201-US-010-0046	329	56	15%
2005NMMF-201-US-010-0048	308	59	16%
2005NMMF-201-US-011-0014	245	105	30%
2005NMMF-201-US-011-0015	241	116	32%
2005NMMF-201-US-012-0016	308	60	16%
2005NMMF-201-US-012-0018	207	105	34%
2005NMMF-201-US-012-0019	224	137	38%

4.2 Clinical Microbiology

Refer to Clinical Microbiology Review.

4.3 Preclinical Pharmacology/Toxicology

Refer to Pharmacology-Toxicology Review.

4.4 Clinical Pharmacology

There were no clinical pharmacology studies conducted that evaluated human pharmacokinetics and pharmacodynamics of mechlorethamine hydrochloride (MCH) 0.02% gel. During the development of topical nitrogen mustard, the Agency recommend for collection of plasma samples to measure MCH concentrations to confirm that there is no systemic exposure to the drug. Per FDA recommendation, the Applicant collected and analyzed blood samples from a total of 38 patients that took part in studies 2005NMMF-201-US and 2007NMMF-202-US. For all plasma samples assayed, the concentrations of MCH and half-mustard were below the limit of quantitation, 5 ng/mL. Thus, there were no measurable concentrations of MCH or half-mustard after 2, 4, or 6 months of daily application of MCH HCL 0.04% gel.

4.4.1 Mechanism of Action

The mechanism of action for topical mechlorethamine for the treatment of mycosis fungoides is not understood.

4.4.2 Pharmacodynamics

Refer to Clinical Pharmacology Review.

4.4.3 Pharmacokinetics

Refer to Clinical Pharmacology Review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

NDA 202317 contained one clinical trial: 2005NMMF-201-US.

Table 3 Tabular Listing of 2005NMMF-201-US

Clinical Trial ID	2005NMMF-201-US
Clinical Trial Title	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)
Clinical Trial Dates	May 2006 to July 2010
Clinical Study Report Status	Final
Support	Efficacy and Safety
Design	Randomized 1:1, active-controlled trial, observer-blinded, multicenter
US Sites	Yes
Dose Regimen	Applied once daily on completely dry skin (at least 4 hours before or 30 minutes after showering)
Number of patients	260

5.2 Review Strategy

The clinical review was based on the efficacy and safety data of 2005NMMF-201-US.
The key review materials and activities are outlined below:
The electronic submission of the NDA;
Relevant published literature;
Relevant submissions in response to information requests;
Applicant presentation slides to FDA on 6 October 2011.
Major efficacy and safety analyses were reproduced or audited.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 2005NMMF-201-US Clinical Protocol

5.3.1.1 Clinical Trial Title

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)

5.3.1.2 Clinical Trial Design

Trial Design

Randomized 1:1, active-controlled trial, observer-blinded, multicenter

Clinical Trial Population

Inclusion Criteria

1. A diagnosis of stage I or IIA (cutaneous only) mycosis fungoides confirmed by a skin biopsy. Patients must not have used steroids for at least four (4) weeks before the diagnostic skin biopsy

2. Diagnostic skin biopsies of MF as determined by both the local site dermato-pathologist and the dermatopathologist at the lead site (Fox Chase Cancer Center) utilizing the histologic criteria previously employed in clinical trials for MF (Duvic 2001) and a diagnostic algorithm for defining early MF developed by the International Society for Cutaneous Lymphoma (ISCL) (Pimpinelli 2005).

3. Stage I and IIA patients must have been treated previously with prior topical therapies including PUVA, UVB, topical steroids, but not NM, or topical carmustine

4. Laboratory values within the range of normal for the participating institution unless the principal investigator feels they are not clinically relevant.

5. Must be free of serious concurrent illness.

6. Must be willing and able to give informed consent, comply with study instructions and commit to all study visits and procedures.

7. Males and females of childbearing potential should be using an effective means of contraception.

Table 4 Staging System for MF in Clinical Trial 2005NMMF-201-US

Stage	TNM Groupings	Description
0	T0, N0, M0	Lesions clinically and/or histologically suggestive of MF. No clinically abnormal peripheral lymph nodes. Pathology negative for MF. No involvement of visceral organs.
IA	T1, N0, M0	Eczematous patches, papules, or limited plaques covering less than 10% of skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for MF. No involvement of visceral organs.
IB	T2, N0, M0	Erythematous patches, papules, or generalized plaques covering 10% or more of the skin surface. No clinically abnormal peripheral lymph nodes, pathology negative for MF. No involvement of visceral organs.
IIA	T1 or T2, N1, M0	Eczematous patches, papules, limited or generalized plaques. Clinically abnormal peripheral lymph nodes with pathology negative for MF. No involvement of visceral organs.
IIB	T3, N0 or N1, M0	One or more cutaneous tumors. Clinically normal or abnormal peripheral lymph nodes with pathology negative for MF. No involvement of visceral organs.
III	T4, N0 or N1, M0	Generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with negative pathology for MF. No involvement of visceral organs.
IVA	T1-T4, N2 or N3, M0	Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology positive for MF. No involvement of visceral organs.
IVB	T1-T4, N0-N3, M1	Eczematous patches, papules, limited or generalized plaques; and/or one or more cutaneous tumors; and/or generalized erythroderma. Clinically normal or abnormal peripheral lymph nodes with pathology negative or positive for MF. Visceral involvement (must have confirmation of pathology; organ involved must be specified).

APPEARS THIS WAY ON ORIGINAL

Exclusion Criteria

1. Newly diagnosed MF with no prior therapy.

2. A prior history of treatment with topical NM or topical carmustine (BCNU).

3. Use of topical or systemic therapies for MF within four (4) weeks of entry in the study.

4. Patients with a diagnosis of stage IIB – IV MF

5. Patients who have a history of a higher T score of T2 or a higher N score of N1.

6. Patients who have had radiation therapy within one year of study start.

7. Any patient who does not agree to do all lab studies at one site (this should be included in Informed Consent).

8. Pregnant or nursing females, or males and females of childbearing potential, not using an effective means of contraception

9. Serious known concurrent medical illness or infection, which could potentially present a safety risk and/or prevent compliance with the requirements of the treatment program.

Diagnostic Criteria for Mycosis Fungoides
Clinical trial 2005NMMF-201-US required confirmation of diagnosis of MF by local and central pathology review, utilizing the histologic criteria (refer to Figure 2), or algorithm criteria (refer to Figure 3).

Reviewer Comment: Algorithm criteria (as outlined in Figure 3 below) was used only in patients who did not meet histologic criteria.

Figure 2 Mycosis Fungoides Diagnosis: Histologic Criteria

1) HISTOLOGICAL CRITERIA FOR MF

Pautrier's Microabscesses:

☐ 0 = None Seen

☐ 1 = One or more histological section

Exocytosis:

☐ 0 = No lymphocytes within epidermis (or spongiotic only)

☐ 1 = Mild degree of exocytosis (1-2 collections of atypical lymphocytes) in the absence of spongiosis

☐ 2 = Moderate degree of exocytosis (>2 collections of atypical lymphocytes but not throughout the epidermis) in the absence of spongiosis

☐ 3 = Diffuse infiltration of many individual atypical lymphocytes through out the epidermis in the absence of spongiosis

Dermal Infiltrate:

☐ 0 = No significant lymphocytic infiltrate

☐ 1 = Mild lymphocytic infiltrate with or without atypical lymphocytes

☐ 2 = Moderate lymphocytic infiltrate with or without atypical lymphocytes

☐ 3 = Marked lymphocytic infiltrate with or without atypical lymphocytes

Papillary dermal fibrosis:

☐ 0 = Normal papillary dermis

☐ 1 = Focal thickening of collagen bundles

☐ 2 = Moderate fibrosis and widening of papillary dermis

☐ 3 = Marked dense fibrosis and markedly widened papillary dermis

Diagnostic of MF = Pautrier score is 1 or Exocytosis score is 3

Consistent with MF = Exocytosis, Dermal Infiltrate, and Papillary dermal fibrosis scores are each at least 2, or if the total score for these 3 criteria is at least 6

*If **Diagnostic of MF** or **Consistent with MF**, subject is eligible for the study.*

Does the biopsy specimen meet the histological criteria? *(see Appendix 2A of the protocol)*

☐ Yes ☐ No → *Complete the Algorithm Diagnosis of Early MF on the next CRF*

Reference: Duvic, 2001

Figure 3 Mycosis Fungoides Diagnosis: Algorithm Criteria

CRITERIA *(check all that apply)*	**SCORING SYSTEM**
CLINICAL **Basic:** ☐ Persistent &/or progressive patches/thin plaques **Additional:** ☐ non-sun exposed skin ☐ size/shape variation ☐ poikiloderma	**CLINICAL** **2 points =** for basic criteria and two additional criteria **1 point =** for basic criteria and one additional criteria **SCORE:** ☐
HISTOPATHOLOGICAL **Basic:** ☐ Superficial lymphoid infiltrate **Additional:** ☐ epidermotropism without spongiosis ☐ lymphoid atypia	**HISTOPATHOLOGICAL** **2 points =** for basic criteria and two additional criteria **1 point =** for basic criteria and one additional criteria **SCORE:** ☐
MOLECULAR BIOLOGICAL ☐ Clonal TCR gene rearrangement	**MOLECULAR BIOLOGICAL** **1 point =** for clonality **SCORE:** ☐
IMMUNOPATHOLOGICAL ☐ < 50% CD2+, CD3+, and/or CD5+ T cells ☐ < 10% CD7+ T cells ☐ epidermal/dermal discordance of CD2, CD3, CD5 or CD7	**IMMUNOPATHOLOGICAL** **1 point =** for one or more criteria **SCORE:** ☐
TOTAL SCORE: ☐ *Add the Clinical, Histopathological, Molecular Biological, and Immunopathological scores.* **Does the biopsy specimen meet the algorithm diagnostic criteria?** *(see Appendix 2B of the protocol)* ☐ Yes ☐ No → *Subject is not eligible for the study*	

Reference: Pimpinelli, 2005

Treatment Plan

All affected areas (lesions) were treated once daily for 12 months, including those who achieve a CR earlier. The frequency of application may be adjusted for toxicity. Patients withdrawn due to progressive disease (>25% worsening) or allergic contact sensitivity (grade 3 or 4 dermal irritation) will be included in the final response assessment.

Patients were evaluated pretreatment (within 90 days of initiation of therapy), baseline (Day 1), every month from months 1-6 and every 2 months from months 7-12. Additional safety and toxicity data were captured for an additional 12 months. After the initial study period of 12 months, treatment will be at the discretion of the physician. However, the patient must continue post-treatment follow up visits for safety monitoring.

Method of Topical Application of NM Ointment. The patient was instructed to apply study drug ointment to all MF lesions daily(refer to Table 5 for specific instructions given to patients). A thin film of ointment was applied to each lesion and application to uninvolved skin should be as limited as possible. A thin film of ointment was applied to localized skin lesions (stage 1A) without deliberate application to unaffected skin.

Total body application was used: 1) to treat diffuse skin lesions (stage 1B or greater) when distinguishing between affected and non-affected areas is impractical; 2) if severity of new lesions developing after treatment initiation meets progressive disease criteria (>25% worsening). The amount of ointment used for each application was dependent upon the amount of body surface area involved. A general measure was that a thin film of ointment will be used to cover surface areas as large as the buttocks.

Five to ten minutes should be allowed after topical ointment application before covering the lesion with clothing. Occlusion at the site of study drug application was not permitted. Daily (QD) applications should be at approximately the same time each day. The ointment should not be removed for a minimum of four hours. However, it does not need to be washed off at all.

After Nitrogen Mustard HCl Ointment has been dispensed it should be kept refrigerated (2-8ºC/36-46ºF). If for any reason Nitrogen Mustard HCl Ointment has been kept at room temperature for more than 20 days, it should be returned to the doctor's office or pharmacy and replaced with a new supply immediately.

Table 5 Instructions for Patient Use of Topical Nitrogen Mustard (copied from 2005NMMF-201-US Protocol)

1. Apply NM ointment only once a day, at least 30 minutes after showering (make sure that you are fully dry) or in the evening, to all of the affected areas of your skin. We recommend application in the evening.
2. Please apply only a very thin film of NM ointment on your skin with each application. A very thin film can be used to cover surface areas as large as the buttocks. Five to ten minutes should be allowed after ointment application before covering the lesion with clothing. The topical NM is maximally absorbed usually within the first hour after application. You may use additional emollient (moisturizers) two hours before or after application.
3. Please wear disposable gloves and wash your hands after applying the NM ointment. The NM ointment does NOT get absorbed into your blood and does NOT result in systemic toxicity. If someone else helps apply the NM, they should wear disposable gloves. If the medicine gets on the skin of the other person, have them wash with soap and water; they will not be affected adversely.
4. In the initial month of NM application, you may see new areas of mycosis fungoides patches show up. The NM can bring out faint, subtle lesions that will become more visible. Please continue the application to these “new” areas until you are seen for a follow-up visit.
5. An irritant contact dermatitis (irritating, itchy rash) is most common and can be seen in up to 25% of individuals using topical nitrogen mustard, particularly if used in sensitive areas such as the face or skin folds. Allergic contact dermatitis (poison ivy-like) reactions occur less frequently (less than 5%).
6. If you are concerned about an irritant reaction or a possible allergic reaction, please discontinue the application and call us, so that we can advise you appropriately. Always, feel free to contact us if you have any questions.
7. After Nitrogen Mustard HCl Ointment has been dispensed, it should be kept refrigerated (2-8°C / 36-45°F).
8. If for any reason, the Nitrogen Mustard HCl Ointment has been kept at room temperature conditions for more than 20 days, it should be returned to your doctor’s office or pharmacy and replaced with a new supply immediately.
9. Please do not throw away any containers of medicine. These must be returned to your doctor’s office or pharmacy.

Treatment Adjustment. Treatment-limiting toxicity (TLT) was defined by the protocol as any treatment-related Grade 3 or higher local dermal irritation as defined in Table 6. Patients who exhibit TLT should have their treatment exposure reduced or discontinued. Emollients and/or oral antihistamines may be used to treat irritant or allergic contact dermatitis, but topical steroids are prohibited. If no frequency of study drug application is tolerated for any of the patient's lesions, then the patient must be withdrawn from the clinical trial.

Table 6 Local Dermal Irritation Grading and Treatment Adjustments

Grade	Defining Clinical Signs	Treatment Adjustments
0 = No Reaction	None	No action required; observation; treatment continues.
1 = Mild	Definite pink to red coloration	
2 = Moderate	Increased redness, with and without edema	
3 = Moderately Severe	Very red, with edema and vesiculation	Treatment frequency should be reduced or suspended for up to two (2) weeks. If after irritation improves to Grade 2 or lower, and treatment is restarted, treatment frequency may be increased every week as tolerated. Patient should be patch tested no sooner than one (1) week off treatment. Positive patch test associated with Grade 3 reactions- treatment is discontinued and patient withdrawn.
4 = Severe	Deep red, swelling and edema with bullae formation and necrosis	Treatment must be discontinued until irritation improves to Grade 2 or lower (this must occur within four (4) weeks); treatment may then be restarted at <QD for at least one (1) week before increasing frequency, as tolerated. Treatment should not be restarted if Grade 4 toxicity occurred at <QD. Positive patch test associated with Grade 4 reactions- treatment is discontinued and patient withdrawn.

Patients with Grade 3 reactions were to suspend application for one week and patch tested, one week off treatment. If patch testing is positive, the patient is withdrawn. If patch testing is negative and local irritation improves to Grade 2 or lower, patients would resume treatment at a frequency of every three day application for up to one week, then every other day application for up to one week, then resume daily applications.

If local irritation reaches Grade 4 reaction, treatment must be discontinued until irritation improves to Grade 2 or lower (this must occur within four weeks). Treatment may then be restarted at less than once daily basis for at least one week before increasing frequency, as tolerated. Treatment should not be restarted if Grade 4 toxicity occurred at less than once daily dosing. If positive patch testing is associated with Grade 4 reactions, the patient should be withdrawn.

Treatment Termination. Progression of disease and/or deleterious changes in the patient's health, which occur during the study, may require termination of treatment and withdrawal from the study. The investigator must consider the patient's best interest and document the specific reasons and rationale for continuing treatment under such circumstances. The occurrence of severe or treatment-limiting toxicity may require that treatment be stopped and that the patient be discontinued from the study. If a patient discontinues the study due to an adverse event, the adverse event will be followed even if not thought to be drug-related at the time.

Criteria for terminating study therapy include, but are not limited to, the following:

- Treatment termination criteria as presented in Table 6
- Positive patch test and grade 3 or 4 dermal irritation
- Concurrent illness which prevents further treatment with NM ointment
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the Investigator.
- The patient or patient's physician is free to discontinue treatment and take the patient off study at any time, especially if this is believed to be in the patient's best interest.

Response Assessment

Composite Assessment of Index Lesion Disease Severity (CAILS) Score. Response assessments of MF index lesion clinical signs will be made at baseline and at every subsequent scheduled visit during treatment.

Up to a maximum of five (5) MF lesions will be designated as index lesions. If the patient has five or fewer MF lesions, then all MF lesions will be designated as index lesions. If the patient has more than five MF lesions, then five lesions that are representative of the patient's overall cutaneous disease will be designated as index lesions. The index lesions should preferably be separate and distinct from other lesions in order to minimize the chance of lesion confluence.

The index lesions will be designated by the letter "X" and numbered in sequence, starting with 1 (i.e., 1X, 2X, 3X, 4X and 5X). The location of all index lesions will be clearly noted on the anatomic chart in the patient's Case Report Form.

Individual index lesion clinical signs will be graded at each visit according to the scales found in Table 7. A CAILS will be generated by a summation of the grades for each index lesion erythema, scaling, plaque elevation, and area. The CAILS grade at baseline will be divided into the CAILS grade at each subsequent study visit to determine the patient's response to treatment.

To determine the area of index lesions, the longest diameter and the longest diameter perpendicular to this diameter of each index lesion will be measured to the nearest millimeter. The lesion area will be the product of these two diameters and then graded as in Table 7. If there is central clearing of an index lesion (clearing of disease within the outer boundaries of the lesion), then the product of the largest perpendicular diameters of the area(s) of clearing will be subtracted from the area determined from the outer boundary diameters before assigning the appropriate grade as in Table 7.

Erythema, scaling and plaque elevation were assessed and graded as in Table 7. The greatest elevation of plaque within a given index lesion should be used in assessing the plaque elevation of that index lesion. If pigmentation obscures all signs of possible erythema, then erythema should be recorded as grade 0.

Table 7 Components of Modified CAILS Score (Composite Assessment of Index Lesion Severity)

SCALING	0 - No evidence of scaling on the lesion	**INDEX LESION AREA**	0 - 0 cm^2 (no measurable area)
	1*		1 - > 0 and ≤ 4 cm^2
	2 - Mild: Mainly fine scales; lesion partially covered		2 - > 4 and ≤ 10 cm^2
	3*		3 - >10 and ≤ 16 cm^2
	4 - Moderate: Somewhat coarser scales; lesion partially covered		4 - >16 and ≤ 25 cm^2
	5*		5 - >25 and ≤ 35 cm^2
	6 - Severe: Coarse, thick scales; virtually all of the lesion covered; rough surface		6 - >35 and ≤ 45 cm^2
	7*		7 - >45 and ≤ 55 cm^2
	8 - Very severe: Coarse, very thick scales; all of the lesion covered; very rough surface		8 - > 55 and ≤ 70 cm^2
ERYTHEMA	0 - No evidence of erythema, possible brown hyperpigmentation		9 - >70 and ≤ 90 cm^2
	1*		10 - >90 and ≤ 110 cm^2
	2 - Mild: Light red lesion		11 - >110 and ≤ 130 cm^2
	3*		12 - >130 and ≤ 155 cm^2
	4 - Moderate: Red lesion		13 - >155 and ≤ 180 cm^2
	5*		14 - >180 and ≤ 210 cm^2
	6 - Severe: Very red lesion		15 - >210 and ≤ 240 cm^2
	7*		16 - >240 and ≤ 270 cm^2
	8 - Very severe: Extremely red lesion		17 - >270 and ≤ 300 cm^2
PLAQUE ELEVATION	0- No evidence of plaque above normal skin level		18 - >300 cm^2
	1- Mild elevation		
	2- Moderate elevation		
	3 – Marked elevation		

* Intermediate intervals 1,3,5 and 7 are to serve as mid-points between the defined grades 0,2,4,6 and 8.

Reviewer Comment: Standard CAILS score includes the following components for each lesion: scaling, erythema, plaque elevation, hypo/hyperpigmentation, and lesion size. Each component is graded from a scale of 0-8 with the exception of lesion size which is graded from 0-18 as described in Table 7.

Severity Weighted Assessment Tool (SWAT) Score. Global response assessments of MF lesions will be made at baseline (Day 1) and at every subsequent scheduled visit during treatment. The SWAT score, a determination of the percentage involvement of total body surface area, and, if present, assessment of clinically abnormal lymph nodes (≥1 cm diameter), will be completed at baseline (Day 1) and at each follow-up visit throughout the study and at follow-up.

The SWAT captures both the extent and severity of skin disease on a continuous numerical scale, and provides a defined, objective, and sensitive quantitative measure of disease status. An assessment of the patient's overall response to topical NM therapy is made as a comparison of the SWAT scores to the cutaneous condition at baseline (study entry).

The severity of skin involvement is classified into three grades based on clinical lesions: 1 for patch disease and erythroderma with mild infiltration; 2 for plaques and erythroderma with moderate infiltration; 3 for cutaneous tumors or ulceration (including fissuring) and erythroderma with tumorous infiltration. The percent body surface area (%BSA = 0% to 100%) affected by each of the three lesion types is measured (The patient's palm will be defined as 1% of that patient's total body surface area). Severity weighting is achieved by multiplying the area for patches by 1, the area for plaques by 2, and the area for tumors or ulcers by 3.

Reviewer Comment: Modified SWAT uses 4x correction factor for tumor. In this application, use of 3x correction factor is highly unlikely to influence the efficacy results as the population studied were patients with patch- and plaque- only disease.

Total BSA. To make this determination, the area of the patient's palm will be defined as 1% of that patient's total body surface area. The extent of involvement of disease should be determined as multiples of the patient's palm area and expressed as a percentage of that patient's total body surface area at baseline (Day 1) and at each study visit for as long as the patient remains on treatment.

Reviewer Comment: A comparison of response criteria used in this clinical trial to the 2011 response criteria for MF is provided in Table 8.

Table 8 Comparison of Skin Response Criteria

	CAILS Response per 2005NMMF-201-US Protocol	SWAT Response per 2005NMMF-201-US Protocol	2011 Skin Response Criteria
Complete Response (CR)	No evidence of disease; 100% improvement. CAILS Score of 0.	No evidence of disease; 100% improvement. SWAT score of 0.	100% clearance of skin lesions.
Complete Clinical Response (CCR)	No evidence of disease; 100% improvement (CAILS Score of 0) plus evidence of histologic clearing.	No evidence of disease; 100% improvement (SWAT score of 0) plus evidence of histologic clearing.	Not defined
Partial Response (PR)	Partial but incomplete clearance ($\geq$ 50%); evidence of disease remains. Final CAILS score of $\geq$ 50% reduction from baseline.	Partial but incomplete clearance ($\geq$50%); evidence of disease remains. Final SWAT score of $\geq$ 50% reduction from baseline.	50-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease.
Stable Disease (SD)	Disease has not changed from baseline condition. A Final CAILS score of < 50% reduction from baseline score.	Disease has not changed from baseline condition. A final SWAT score of < 50% reduction from baseline score.	<25% increase to <50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease.
Progressive Disease (PD)	Disease is worse than at baseline evaluation by a CAILS score of $\geq$ 25% increase from baseline.	Disease is worse than at baseline evaluation by a SWAT score of $\geq$ 25% increase from baseline.	$\geq$ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than sum of nadir plus 50% baseline score.

Reference: Olsen, 2011

5.3.1.3 Clinical Trial Landmarks and Protocol Amendments

The protocol for clinical trial 2005NMMF-201-US had 5 amendments. A summary of non-administrative amendments and clinical trial landmarks are summarized below.

Table 9 Protocol Amendments for 2005NMMF-201-US

Date	Cumulative Number of Patients Randomized	2005NMMF-201-US Landmark
6 Jan 2006	0	**Original protocol**
7 Mar 2006	0	**Amendment 1** - Deleted quality of life (QOL) questionnaire
9 Jan 2007	34	**Amendment 2** - Mid- and post-treatment biopsies no longer required.
9 Apr 2007	56	**Amendment 3** - There had to be concordance on the diagnosis of early MF between the local and central dermatopathologist. - Requirement for mid- and post-treatment skin biopsies was eliminated. - Clarified language in protocol for: Prior BCNU was not permitted, Prior NM was permitted if at least 2 years had elapsed - Clarified patient instruction to "Apply NM ointment only once a day, at least 30 minutes after showering (make sure that you are fully dry) or in the evening to all of the affected areas of your skin."
13 Mar 2008	134	**Amendment 4** - Sample size increased from 118 patients to 200 patients, in recognition that CAILS response rates closer to 70% than initial assumption of 84% - Instructions to patients amended: "After Nitrogen Mustard HCl Ointment has been dispensed it should be kept refrigerated (2-8°C/36-45°F). If for any reason, Nitrogen Mustard HCl Ointment has been kept at room temperature for more than 20 days, it should be returned to your doctor's office or pharmacy and replaced with a new supply immediately." - Clarified language in protocol for: No other treatments for MF were permitted, Post treatment follow-up for 12 months to capture additional safety data (including monitoring for squamous cell carcinoma)
8 Dec 2008	198	**Amendment 5** - Sample size increased from 200 patients to 250 patients.

Schedule of assessments

Table 10 Schedule of Assessments

ASSESSMENT TO BE COMPLETED	Pre-Study Up to 90 days Before Day 1	Pre-Study Up to 30 days Before Day 1	Prior to Day 1	Day 1 "Baseline" 1st Rx Day	Week 4	Every Month to Month 6 Every 2 Months To Month 12	Extended Tox Evaluation for an additional 12 months
MF Confirmed by Biopsy	X (NOTE 2)			X		X	
Symptoms and/or AEs	X			X		X	
Med History/Physical Exam	X			X		X	X (NOTE 5)
No Serious Concurrent Illness or Infection	X			√		√	
LABORATORY							
Chemistry Panel and CBC	X (NOTE 1)					X (NOTE 4)	
Plasma Nitrogen Mustard/Half Mustard (select sites only)				X (NOTE 3)	X (NOTE 3)		
Serum pregnancy test		X					
EFFICACY							
CAILS & SWAT				X		X	
Body Surface Area Involvement				X		X	
Clinical Photographs				X		X (NOTE 6)	
Randomization/Patient Numbers			X				

"X" = Required "√" = Check on Status

NOTE 1: "Pre-study" assessments must be obtained and results known prior to randomization. Can use previous labs if obtained within 90 days of Day 1.
NOTE 2: Skin (punch) biopsy of a lesion pre-study only. Can use previous biopsy if obtained within 90 days of Day 1. It still must be evaluated locally and at confirmatory site.
NOTE 3: Serum for drug levels will be drawn on Day 1 (at 0, 1, 3, 6 hrs after application) and at 4 weeks (one time) on 30 patients.
NOTE 4: Completed at months 1, 4, 8, and 12 only.
NOTE 5: Clinical documentation of skin cancers (type & location), unresolved AEs, quarterly visits for an additional 12 months.
NOTE 6: Global photographs are to be obtained at baseline, subsequent visits demonstrating response/progression, and final visit; Close-up photographs of index lesions will also be obtained at baseline, subsequent visits response/progression, and final visit.

5.3.1.4 Efficacy and safety evaluation

The intent-to-treat population consisted of all randomized patients. The intent-to-treat population was the primary population for the efficacy analysis.

The safety population was defined as patients who had taken the study medication. The safety population was used as the basis for the summarization of laboratory and adverse event data.

5.3.1.5 Statistics

5.3.1.5.1 Sample Size

The response rate (complete and partial response from the Composite Assessment of Index Lesion Disease Severity) was initially estimated to be approximately 84% for patients to be enrolled to this study. Using the sample size calculations based on the non-inferiority hypothesis that the ratio of the response rates (PG formulation compared to the AP formulation) should be no less than 0.75, i.e. a minimum 75% retention of effect, with 80% power and a 95% confidence interval for the estimate of the ratio, between 45 and 55 subjects are required given the response rate for the AP formulation is between 84% and 80%.

Sample size was increased to final of 250 patients in recognition that the CAILS response rates would be closer to 70% compared to the initial assumption of 84%.

Patients were stratified by their initial MF stage into two randomization strata. The first stratum will be for patients assessed with stage IA MF. The second stratum will be those patients assessed to have either stages IB or IIA MF. Within each stratum the patients will be randomized to receive either the PG or AP formulation of NM 0.02%. The purpose of this stratification is to ensure an equal representation of both treatment groups within a given stratum and the randomization code will be structured accordingly.

5.3.1.5.2 Endpoints and Efficacy Analyses

Primary Endpoint
The primary efficacy variable will be the indication of a complete or partial response determined by the Composite Assessment of Index Lesion Disease Severity within up to 12 months of study drug application by two or more consecutive observations over at least four weeks.

Non-inferiority will be assessed based on the 95% confidence interval around the ratio of the response rate of the patients treated with the PG formulation to the response rate of the patients treated with the AP formulation. This will be calculated using the

likelihood ratio methods of Miettinen and Nurminen (1985). The PG formulation will be determined to be non-inferior to the AP formulation if the lower limit of the 95% confidence interval is ≥0.75.

Secondary Endpoints

According to Statistical Analysis Plan, recommended control for multiple testing among the secondary efficacy endpoints using the a type I error rate of 0.010 for each endpoint.

1. SWAT Score
This efficacy variable will be the indication of a complete or partial response determined by the SWAT score within up to 12 months of study drug application by two or more consecutive observations over at least four weeks.

2. Extent of Cutaneous Disease
The total percentage body surface area component of the SWAT score calculation will be used as a measure of the overall extent of cutaneous disease. Changes from baseline to the final assessment in the percentage body surface area involvement will be compared between the two treatment groups using the subject's initial value as covariate.

3. Time to Response
The time to response for a given patient is defined as the time interval from the first day NM ointment was applied to the time of the first observation when the patient meets the criteria for CR or PR by the assessment of Composite Assessment of Index Lesion Disease Severity. For complete or partial response this is the date of the evaluation at least 28 days after the first assessment of complete or partial response which also shows a similar response sustained for at least that period of time with no intervening assessments indicating otherwise.

4. Response Duration
For those patients who show a response (complete or partial) by assessment of the Composite Assessment of Index Lesion Disease Severity, the duration of the response will calculated as the time from the first appearance of the response to the first assessment where the response is no longer apparent. When the final assessment still shows a response then the time will be taken to that response and the value censored to the right (i.e. recorded as greater than that duration). When multiple periods of response are indicated for a given patient, the maximum uncensored period will be used in the analysis.

5. Time to Progression
The time to progression for each patient will be calculated from the first day NM ointment was applied to the date the first disease progression occurred (25% or

greater increase in Composite Assessment of Index Lesion Disease Severity from that recorded at baseline). When the patient has no disease progression, the date of the last assessed Composite Assessment of Index Lesion Disease Severity will be used and the value will be included in the analysis as a right censored value.

5.3.1.5.3 Safety Analyses

Treatment compliance and frequency were summarized and listed. Dose modifications were also summarized and listed.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 8.1). Summary tables were presented by primary system organ class and preferred term. AE Severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE v3).

Serious adverse events were listed and summarized in the same manner as all AEs. Events with a fatal outcome were listed.

Laboratory parameters (CBC, biochemistry) at each treatment time point, and their change from baseline were summarized. Time intervals were defined to assign the laboratory values to the planned month 1, 4, 8 and 12 sample times.

6 Review of Efficacy

Efficacy Summary

The efficacy of Valchlor was evaluated in 242 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key efficacy results from this non-inferiority clinical trial are listed below.

- The primary endpoint was CAILS response (based on maximum of 5 index lesions per patient). Secondary endpoints include SWAT response (global response), duration of CAILS response, time to CAILS response, and time to CAILS progression. Non-inferiority to active control would be demonstrated if the lower limit of the 95% confidence interval of response rate ratio (Valchlor:control) is ≥ 0.75.

- Clinical trial 2005NMMF-201-US achieved its primary endpoint. The CAILS response rate ratio was 1.24 with 95%CI of 0.98 to 1.58. The CAILS response rate was 60% in Valchlor arm and 48% in control arm.

- Secondary endpoints supported the primary endpoint result.
  - The SWAT response rate ratio was 1.07 with 95%CI of 0.82 to 1.39. The SWAT response rate was 50% in the Valchlor arm, and 46% in the control arm.
  - Time to CAILS response and time to SWAT response were similar between treatment arms. Median time to response (CAILS or SWAT) was 4 months for the Valchlor arm, and 3 months for the control arm.
  - Duration of CAILS response and duration of SWAT response were similar between treatment arms. Median duration of response (CAILS or SWAT) was not reached.

- The trial population consisted of 242 patients enrolled from U.S. sites. Patients were required to have central and local pathology confirmation of the diagnosis of mycosis fungoides. All patients had at least one prior therapy. There was similar distribution of demographic parameters (gender, age, race) and baseline disease characteristics (stage of disease, duration of disease, prior therapies) between treatment arms.

However, due to inadequate product quality characterization of clinical trial lots of Valchlor (refer to Section 4.1), the above efficacy results cannot be extrapolated to the proposed commercial product lots of Valchlor. The applicant will need to conduct one or more clinical trials to establish the efficacy of commercial product lots of Valchlor.

6.1 Indication

The applicant's proposed indication 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)

Reviewer Comment: If complete responses issues were not identified, this reviewer would have recommended an indication for the topical treatment of cutaneous lesions in patients with Stage I mycosis fungoides type cutaneous T-cell lymphoma (CTCL) who have received at least one prior skin-directed therapy.

(b) (4)

All patients had at least one prior skin-directed therapy in the clinical trial. Eighty-eight percent had prior topical corticosteroid exposure. However, because none of the topical corticosteroids have a specific indication for CTCL, reference to topical corticosteroids in the proposed indication is not recommended.

The term "mycosis fungoides type CTCL" in the indication is acceptable. CTCL includes other subtypes such as primary cutaneous anaplastic large cell lymphoma, primary cutaneous peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma, and angioimmunoblastic T-cell lymphoma. Although previous approvals for CTCL do not specify mycosis fungoides, inclusion of term "mycosis fungoides type" in the CTCL indication is an accurate and appropriate description for the population studied in the clinical trial.

6.1.1 Methods

The efficacy review for Valchlor was performed by review of the following items submitted by the Applicant (Yaupon Therapeutics, Inc.):

- Summary of Clinical Efficacy
- Protocol and Statistical Analysis Plan for 2005NMMF-201-US
- Clinical study report for 2005NMMF-201-US
- Raw and derived datasets for 2005NMMF-201-US
- Case report forms for 2005NMMF-201-US
- Patient photographs for 2005NMMF-201-US
- Response to Information Requests
- Proposed labeling for Valchlor

As discussed in Section 5.3.1.4, the primary population for efficacy analysis is the intent-to-treat (ITT) population consisting of all randomized patients (N=260). However, because of major protocol violation involving randomization at Site 7 (New York University), the ITT population for primary efficacy analysis excludes the NYU site, for a final efficacy population size of 242 patients.

The randomization violation at Site 7 (NYU) involved the unblinded study coordinator assigning study treatment (Yaupon versus control formulation) based on disease stage rather than randomization code. She assigned Drug A (Yaupon formulation) to all patients in stratum one (Stage IA disease) and Drug B (control formulation) to all patients in stratum two (Stage IB or IIA disease). This error occurred in the first 16 patients randomized. Once the error was discovered, the investigator was unblinded, and remained unblinded throughout the remainder of the clinical trial. A total of 18 patients were accrued at Site 7.

When this problem was discovered at NYU, the randomization procedures followed at all other sites were reviewed and monitored by a Yaupon employee other than the site CRA. Yaupon confirmed that all other sites randomized patients correctly. Subsequent monitoring visits also verified that the investigators remained blinded to treatment.

Reviewer Comment: Site 7 (NYU) patients are not considered part of the ITT population because the randomization procedure at that site was not followed intentionally by the study coordinator, thus nullifying the effect of randomization. Whether some of the patients at Site 7 received the treatment as randomized is irrelevant, as the intent to randomize was not based on the randomization code.

6.1.2 Demographics

Clinical trial 2005NMMF-201-US enrolled 260 patients from 13 sites in the United States. The ITT population consisted of 242 patients from 12 sites due to major protocol violation on randomization at the NYU site.

Table 11 Sites of Enrolment

Site Name	Yaupon Arm	Control Arm	Total
MD Anderson Cancer Center	30	32	62 (26%)
Northwestern University	22	22	44 (18%)
Stanford University	20	18	38 (16%)
University of Texas Southwestern	10	11	21 (9%)
Duke University	8	10	18 (7%)
Fox Chase Cancer Center	8	7	15 (6%)
Utah Clinical Trials	7	7	14 (6%)
Columbia University	5	4	9 (4%)
Hospital of the University of Pennsylvania	4	3	7 (3%)
Oklahoma University	1	6	7 (3%)
Brigham & Women's Hospital	3	1	4 (2%)
University of Wisconsin	1	2	3 (1%)
Total	**119**	**123**	**242 (100%)**

The demographics of the 242 patients in the ITT population is summarized in Table 12. Gender, age, and race distributions were balanced between treatment arms. About 60% of the patients were male. The median age was 57 years in the Valchlor arm, and 58 years in the control arm. The age range was 24 to 83 years in Valchlor arm, and 11 to 88 years in control arm. Seventy-five percent of the trial population were Caucasian.

Table 12 Demographics of ITT Population

Demographic Parameter	**PG (Yaupon) N = 119**	**AP (Control) N = 123**
Gender		
Male	71 (60%)	72 (59%)
Female	48 (40%)	51 (41%)
Age (years)		
Mean (SD)	54.4 (14.5)	56.4 (14.5)
Median	57	58
Range	24 to 83	11 to 88
Groups		
<18	0	1 (1%)
18 to 39	26 (22%)	17 (14%)
40 to 64	59 (50%)	64 (52%)
≥ 65	34 (29%)	41 (33%)
Race		
Caucasian	89 (75%)	92 (75%)
African-American	15 (13%)	17 (14%)
Asian	4 (3%)	3 (2%)
Other	11 (9%)	11 (9%)

Baseline Disease Characteristics

Baseline disease characteristics are summarized in Table 13. Disease duration and stage were balanced between treatment arms. The clinical trial population included patients with varying durations of disease, ranging from less than 6 months (36% in Valchlor, 34% in control) to patients with ≥ 2 years of disease duration (39% in Valchlor, 38% in control).

Majority of patients (~55%) in both treatment arms had Stage IA disease, defined as less than 10% skin involvement (T1–patches and plaques only), no nodal or systemic involvement. Randomization was stratified by disease stage. Strata 1 included patients with Stage IA disease. Strata 2 included patients with Stage IB or IIA disease. Stage IB includes patients with more than 10% skin involvement (T2–patches and plaques only), no nodal or systemic involvement. Stage IIA includes patients with T1 or T2 skin

involvement, with lymphadenopathy (pathology negative for MF), and no systemic involvement.

Assessments of baseline disease status (CAILS, SWAT, and BSA scores) were similar between treatment arms. The number of skin lesions per patient chosen for the CAILS response endpoint is shown in Table 14.

Table 13 Baseline Disease Characteristics

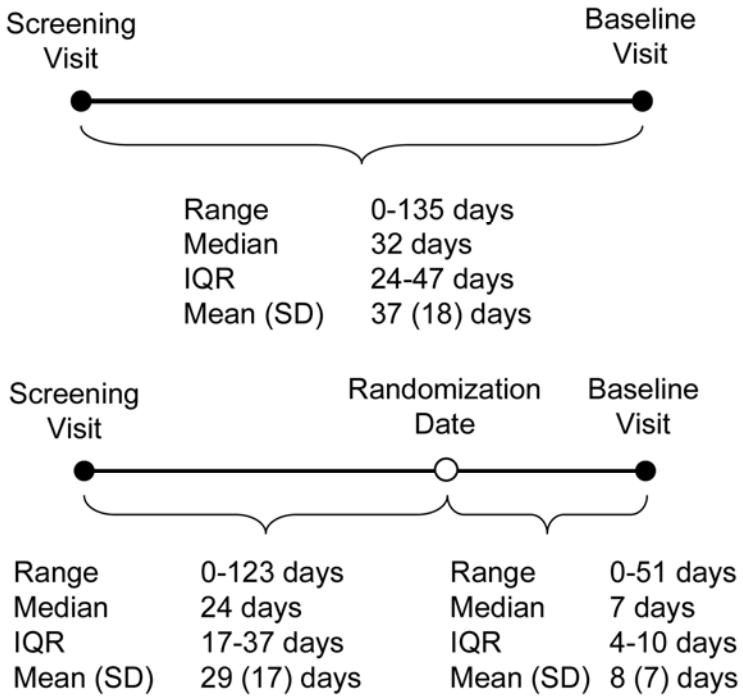
Mycosis Fungoides	**PG (Yaupon) N = 119**	**AP (Control) N = 123**
Duration of Disease		
Less than 6 months	43 (36%)	42 (34%)
≥ 6 months to <2 years	30 (25%)	34 (28%)
≥ 2 years	46 (39%)	47 (38%)
Disease Stage, at Final Randomization		
IA	65 (55%)	64 (52%)
IB	52 (44%)	57 (46%)
IIA	2 (2%)	2 (2%)
CAILS Score, baseline visit		
Mean (SD)	38 (17)	37 (18)
Range	2-79	6-87
Median (IQR)	36 (25-50)	33 (24-47)
SWAT Score, baseline visit		
Mean (SD)	15 (16)	18 (19)
Range	1-104	1-104
Median (IQR)	9 (4-21)	11 (5-25)
BSA involvement, baseline visit		
Mean (SD)	13 (12)	16 (15)
Range	1-61	1-76
Median (IQR)	9 (4-19)	9 (4-23)

Reviewer Comment: CAILS score appeared to provide a more granular assessment of disease status compared to SWAT or BSA. Median CAIL scores at baseline was 33-36 compared to 9-11 for baseline SWAT or BSA. CAILS and SWAT responses should be interpreted together due to the limitations of CAILS score due to its scope (maximum of 5 lesions per patient) as compared to global assessments such as SWAT or BSA.

Table 14 Number of Index Lesions Selected for CAILS Score

Number of Index Lesions Selected for CAILS Score	Yaupon Arm (N=119)	Control Arm (N=123)	Total (N=242)
5	63 (53%)	53 (43%)	116 (48%)
4	10 (8%)	19 (15%)	29 (12%)
3	43 (27%)	34 (28%)	66 (27%)
2	8 (7%)	10 (8%)	18 (7%)
1	5 (4%)	4 (3%)	9 (4%)
Missing	1 (1%)	3 (2%)	4 (2%)

Figure 4 Interval between Screening Visit, Original Randomization Date, and Baseline Visit



The interval between the screening visit to the start of treatment lasted up to 135 days. The interval between randomization to the start of treatment lasted up to 51 days. A summary of the interval between the screening visit, original randomization, and start of treatment is shown in Figure 4.

Twenty two (9%) of the 242 patients (7 in Valchlor arm, 15 in control arm) had a change in the mycosis fungoides stage from the time of randomization to start of treatment (refer to Table 15 and Table 16). Five patients were no longer eligible for the trial as a result of disease status change (1 patient developed tumor-stage skin disease; 4 patients were listed as progressive disease with no other details provided). Sixteen patients had a change in MF stage which resulted in change in randomization strata; 8 of the 16 patients were re-randomized, the other 8 remained with the original randomization. Two patients had a change in stage not resulting in change in randomization strata (Stage IIA → IB). All of the 22 patients with change in disease stage are included in the ITT population as all of these patients underwent randomization.

Reviewer Comment: The re-randomization of 8 patients due to change in disease stage is acceptable because the patients were not aware of the original randomization and none had started treatment at the time of rerandomization.

Table 15 Stage Migration from Randomization to Baseline Visit (Valchlor)

Valchlor	**Disease Stage at Baseline Visit**			
Disease Stage at Randomization	**IA**	**IB**	**IIA**	**Progressed beyond IIA**
IA	61	3	0	1
IB	2	49	0	1
IIA	0	0	2	0

Table 16 Stage Migration from Randomization to Baseline Visit (Control Arm)

Control Arm	**Disease Stage at Baseline Visit**			
Disease Stage at Randomization	**IA**	**IB**	**IIA**	**Progressed beyond IIA**
IA	57	6	0	2
IB	5	50	0	1
IIA	0	2	0	0

Prior Therapies
All patients had at least one prior therapy for mycosis fungoides. The types and number of lines of prior therapy appear to be balanced between treatment arms (refer to Table 17). The most common prior therapy was topical corticosteroids (88% in Valchlor arm, 86% in treatment arm).

Table 17 Prior Therapies

Prior Therapies	**PG (Yaupon) N = 119**	**AP (Control) N = 123**
Number of Lines of Prior Therapy		
At least 1	100%	100%
Range	1-23	1-10
Median	2	2
IQR	1-4	1-3
Prior Therapy		
Corticosteroids	88%	86%
Phototherapy	38%	40%
Targretin	18%	18%
Topical nitrogen mustard	13%	10%
Other topical retinoid	4%	8%
Topical calcineurin inhibitor	2%	6%
Imiquimod	2%	4%
Interferon	3%	4%
Methotrexate	3%	2%
Radiation	3%	2%

6.1.3 Subject Disposition

The applicant classified reasons for withdrawal into treatment limiting toxicity, adverse event, lack of efficacy, subject's best interest, concurrent illness, withdrew consent, non-compliance, lost to follow-up, and other. The Agency adjudicated the patient disposition to address splitting (e.g., treatment limiting toxicity and adverse event; lack of efficacy and progressive disease), and to combine related events (e.g., reason for discontinuation coded as "Other", but verbatim term is adverse event).

Patient disposition is summarized in Table 18. The frequency and reasons for treatment discontinuation were similar between treatment arms. For both arms, only 2/3 of the patients completed planned 12 months of treatment.

Adverse event (AE) was the most common reason for treatment discontinuation, occurring in approximately 20% of the patients. Analysis of AE leading to treatment discontinuations is provided in Section 7.3.3.

Table 18 Patient Disposition in ITT Population

Disposition	**Yaupon Arm** (N=119)	**Control Arm** (N=123)	**Total** (N=242)
Completed 12 months of treatment	78 (66%)	83 (67%)	161 (67%)
Discontinued prior to 12 months due to:			
Adverse event	24 (20%)	21 (17%)	45 (19%)
Progressive disease or lack of efficacy	6 (5%)	8 (7%)	14 (6%)
Concurrent illness	5 (4%)	3 (2%)	8 (3%)
Lost to follow-up	2 (2%)	3 (2%)	5 (2%)
Non-compliance	1 (1%)	3 (2%)	4 (2%)
Withdrew consent	2 (2%)	1 (1%)	3 (1%)
Subject's best interest	1 (1%)	0	1 (0.4%)
Other	0	1 (1%)	1 (0.4%)

6.1.4 Analysis of Primary Endpoint

The applicant and FDA analysis of the primary endpoint (CAILS response) showed the same results (refer to Table 19). The ratio of CAILS response rates for the ITT population is **1.24** with 95% CI of 0.98 to 1.58, meeting the protocol defined criterion for non-inferiority.

Table 19 Primary Endpoint Results (CAILS Response)

CAILS Response, N(%)	**PG (Yaupon) N = 119**	**AP (Control) N = 123**
Best Response		
Complete Response (CR)*	17 (14%)	14 (11%)
Partial Response (PR)	54 (45%)	45 (37%)
Stable Disease (SD)	36 (30%)	59 (48%)
Progressive Disease (PD)	5 (4%)	1 (1%)
Unevaluable (UE)	7 (6%)	4 (3%)
Responder (CR+PR)	71 (60%)	59 (48%)
Nonresponder (SD+PD+UE)	48 (40%)	64 (52%)

*See discussion in text regarding limitations of CAILS Complete Response.

Complete Response (CR) using the CAILS criteria is problematic. The CAILS criteria is based on a maximum of 5 index lesions. A patient would be considered a CAILS CR with complete resolution of all 5 index lesions, but may still have remaining disease (non-index lesions), or have developed new lesions. Of the 31 patients who achieved a CAILS CR, only 11 (35%) had a global CR (SWAT response) as well. The remaining 18 patients had PR on SWAT criteria, and 2 patients had SD on SWAT criteria.

Reviewer Comment: This reviewer recommends against reference to CAILS CR in the label, as this concept is not accurate (see discussion above). Categorization to responder vs. non-responder would be an appropriate presentation of the above data.

6.1.5 Analysis of Secondary Endpoints

SWAT Response
The applicant and FDA analysis for SWAT response showed the same results (refer to Table 20). The ratio of SWAT response rates for the ITT population is **1.07** with 95% CI of 0.82 to 1.39, meeting the protocol defined criterion for non-inferiority.

Table 20 SWAT Response in ITT Population

SWAT Response, N(%)	**PG (Yaupon) N = 119**	**AP (Control) N = 123**
Best Response		
Complete Response (CR)	8 (7%)	4 (3%)
Partial Response (PR)	51 (43%)	53 (43%)
Stable Disease (SD)	43 (36%)	45 (37%)
Progressive Disease (PD)	11 (9%)	17 (14%)
Unevaluable (UE)	6 (5%)	4 (3%)
Responder (CR+PR)	59 (50%)	57 (46%)
Non-responder (SD+PD+UE)	60 (50%)	66 (54%)

Time to Response
Time to response was defined by the applicant as time interval from treatment start to the first observation when the patient meets the criteria for CR or PR. The applicant analyzed time to response based on all randomized patients. Patients who did not have a response were censored at the last assessment.

For this endpoint, the Agency analyzed time to response as time interval from time of randomization to the first observation when the patient met the criteria for CR or PR. In contrast to the applicant's analysis, the Agency performed the of time to response analysis in the responder population.

Reviewer Comment: It is not appropriate to include the non-responder population in the time-to-response analysis. In any time-to-event analysis, the outcome of censored patients is represented by the remaining non-censored patients. For example, patients censored for discontinuation due to AE would be represented by patients remaining in the trial, which would be problematic. Another issue would be that censored patients are considered to be at risk for the event, in this case, response. Whether such censored patients can be truly considered to respond even after discontinuation of therapy and attribute this response to specific treatment delivered is problematic. Interpretation of

such results would be complicated by subsequent therapies, and the natural history of the disease.

There was no significant difference in time to response (CAILS or SWAT) between treatment arms. The median time to response in patients in the Valchlor arm was about 4 months (CAILS or SWAT response). For the control arm, the median time to response was approximately 3 months.

Table 21 Time to Response Analysis (CAILS and SWAT)

Time to Response	PG (Yaupon) Treatment Arm	AP (Control) Treatment Arm
Number of CAILS Responses	71	59
Median Time to CAILS Response, months (95% CI)	3.8 (3.0, 5.1)	3.2 (2.5, 4.2)
Number of SWAT Responses	59	57
Median Time to SWAT Response, months (95% CI)	4.0 (3.4, 5.1)	3.3 (2.8, 3.9)

Duration of Response

There was no significant difference in duration of response (CAILS or SWAT) between treatment arms (Table 22). For the Valchlor arm, the median duration of response was 11.5 months for CAILS response and not reached for SWAT response. The median duration of response (CAILS or SWAT) was not reached for the control arm.

Reviewer Comment: The interpretation of duration of response using CAILS criteria is problematic, as the CAILS criteria is limited to the assessment of a maximum of 5 pre-selected index lesions. Evidence of progression in non-index lesions, or development of new lesions cannot be adequately captured by the CAILS criteria. Hence, a patient may be recorded as having durable response based on index lesions, but may have developed progression in non-index lesions, or developed new lesions.

Table 22 Duration of Response Analysis (CAILS and SWAT)

Duration of Response	PG (Yaupon)	AP (Control)
Number with CAILS Response Number with event* Censored	71 11 60	59 11 48
Median Duration of CAILS Response, months (95% CI)	11.5 (11.5, NE)	NE (NE, NE)
Number with SWAT Response Number with event* Censored	59 15 44	57 17 40
Median Duration of SWAT Response, months (95% CI)	NE (8.1, NE)	NE (9.0, NE)

*Event = Loss or Response or Progressive Disease

Figure 5 Kaplan-Meier Curve of Duration of Response

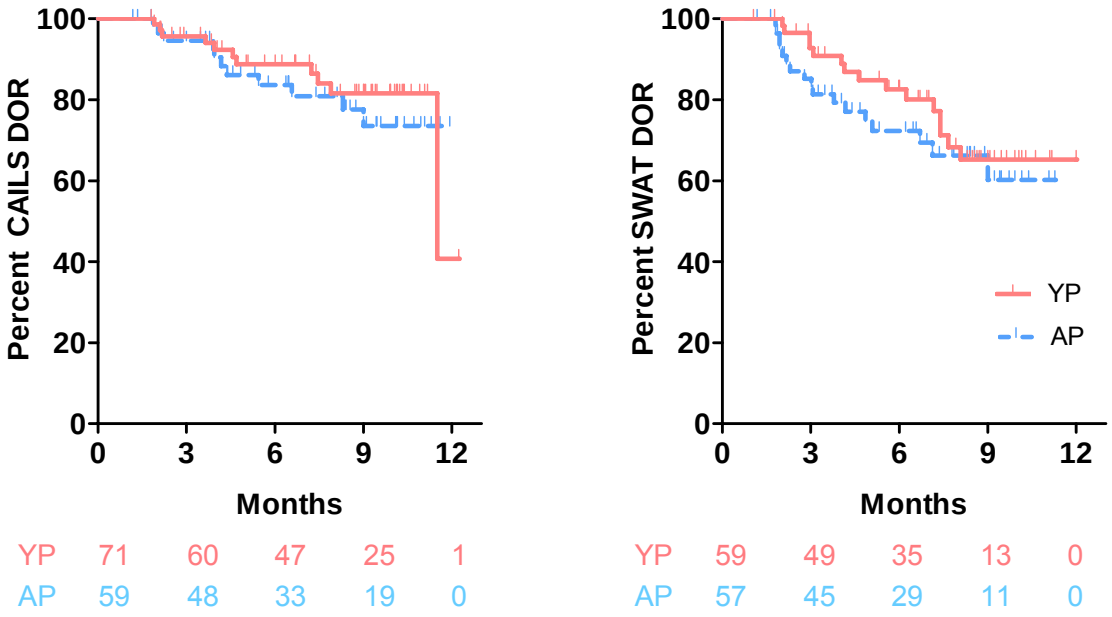
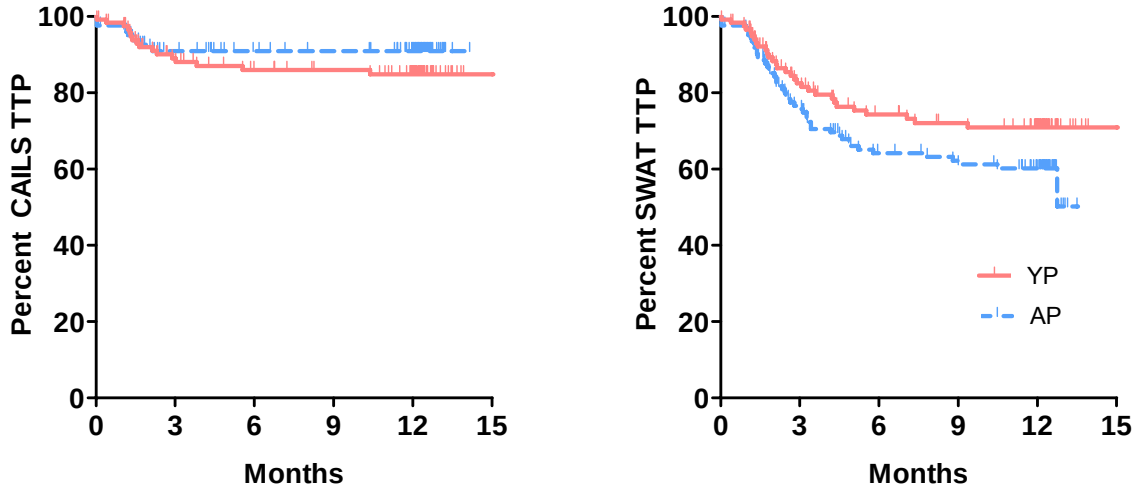


Table 23 Time to Progression Analysis (CAILS and SWAT)

Time to Progression	PG (Yaupon)	AP (Control)
Number of Randomized Patients Number with CAILS Progression Event Censored	119 16 103	123 11 112
Median Time to CAILS Progression, months (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard Ratio for Time to CAILS Progression (PG/AP), (95% CI)	1.59 (0.74, 3.42) P = 0.2339, log-rank	
Number of Randomized Patients Number with SWAT Progression Event Censored	119 30 89	123 47 76
Median Time to SWAT Progression, months (95% CI)	NE (NE, NE)	NE (12.7, NE)
Hazard Ratio for Time to SWAT Progression (PG/AP), (95% CI)	0.66 (0.42, 1.05) P = 0.0759, log-rank	

Figure 6 Kaplan-Meier Curve of Time to Progression



Time to Progression

There was no significant difference in time to progression (CAILS or SWAT) between treatment arms (refer to Table 23). The median time to progression (CAILS or SWAT) was not reached in either treatment arm.

The applicant excluded patients without baseline or follow-up response assessments in their time to progression analysis. The Agency included all randomized patients in the time to progression analysis. Patients without any response assessments were considered to have progression on the day after randomization (4 patients: 02-024, 02-040, 02-051, 10-030).

The definition of progression was the same for CAILS and SWAT criteria: increase by $\geq$ 25% from baseline score. For SWAT criteria, the development of skin tumor stage disease (T3) was included as SWAT progression (4 patients: 01-001, 01-005, 02-038, 09-003).

Reviewer Comment (1): There were more patients who met criteria for progression by SWAT criteria (77 patients) compared to CAILS criteria (27 patients). The difference in the number of progression events between the CAILS and SWAT criteria could be due to higher scores on CAILS criteria on a numerical basis. The absolute magnitude of increase required for progression would be less for SWAT compared to CAILS in this clinical trial. The median baseline CAILS score was about 35 compared to median baseline SWAT of 9. Hence, an absolute magnitude of increase by 3 in a patient with a baseline SWAT score of 9 would qualify as progression.

Reviewer Comment (2): The clinical significance of SWAT or CAILS progression in this patient population is unclear. Patients could continue treatment as planned even with progression in skin involvement (i.e., increase of extent, but not development of skin tumor stage, or systemic disease). Seven of the 27 (26%) patients with CAILS progression subsequently attained a confirmed response. Fifteen of the 77 (19%) of patients with SWAT progression subsequently attained a confirmed response. It is possible that progression early in the treatment course may represent a tumor flare or inflammatory reaction, that eventually subsides, with some patients able to achieve a subsequent response.

Reviewer Comment (3): The interpretation of progression using CAILS criteria is problematic, as the CAILS criteria is limited to the assessment of a maximum of 5 pre-selected index lesions. Evidence of progression in non-index lesions, or development of new lesions is not adequately captured by the CAILS criteria.

6.1.6 Other Endpoints

Concordance between CAILS and SWAT Responses
The concordance between CAILS and SWAT responses in the ITT population was 79%. Patients on the Valchlor arm had 85% concordance in the CAILS and SWAT responses as compared to 74% concordance for the control arm.

Comparison between treatment groups of the number of patients who achieved both CAILS and SWAT responses shows response rates of 47% (56/119, Valchlor arm) and 34% (42/123, control arm). The response rate ratio is **1.38** with a 95% CI of 1.02 to 1.88.

Table 24 Concordance in CAILS and SWAT Responses (ITT Population)

ITT Population (N=242)	SWAT Responder	SWAT Non-responder
CAILS Responder	98	32
CAILS Non-responder	18	94

Table 25 Concordance in CAILS and SWAT Responses (Valchlor Arm)

Valchlor Arm (N=119)	SWAT Responder	SWAT Non-responder
CAILS Responder	56	15
CAILS Non-responder	3	45

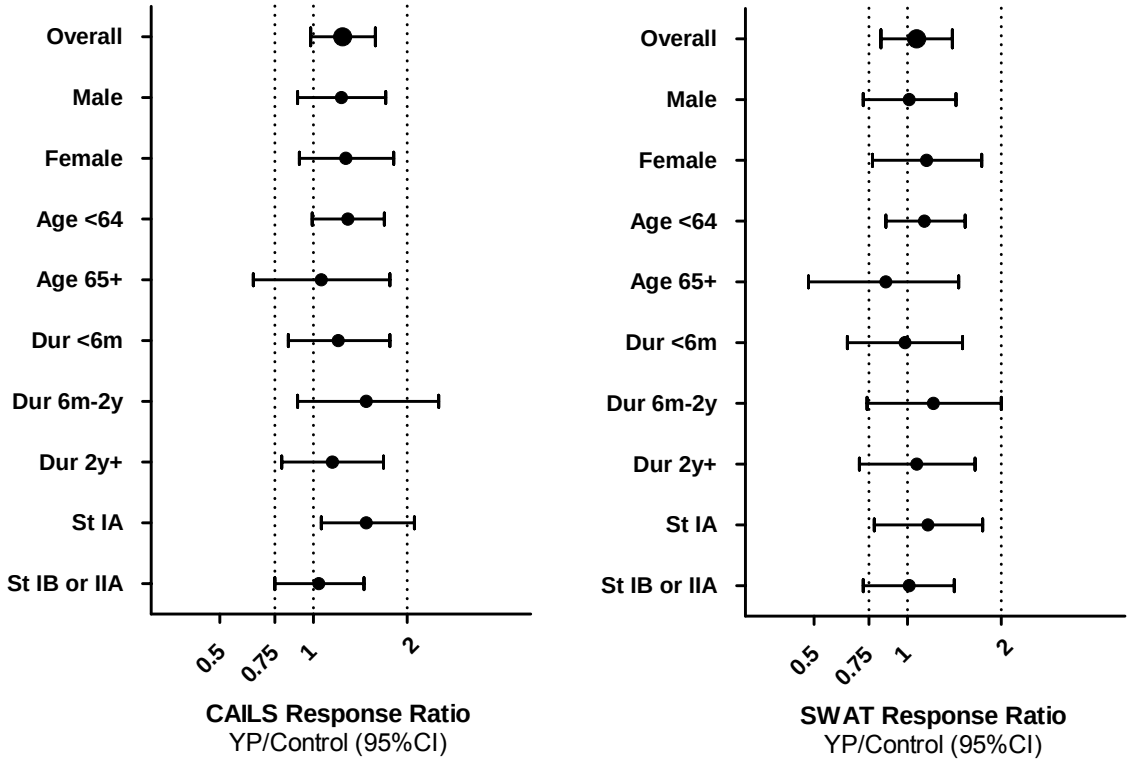
Table 26 Concordance in CAILS and SWAT Responses (Control Arm)

Control Arm (N=123)	SWAT Responder	SWAT Non-responder
CAILS Responder	42	17
CAILS Non-responder	15	49

6.1.7 Subpopulations

The results of subgroup analysis should be interpreted with caution. In addition, the small number of patients (N=242) further limits the analysis by subgroups. In general, results of the subgroup analysis for CAILS and SWAT response shows overlapping confidence intervals for response rate ratios among several subgroups.

Figure 7 Subgroup Analysis for CAILS and SWAT Response Ratios



Reviewer Comment: The lower bound for the 95% CI of CAILS and SWAT response rate ratios appear to be lower in the age 65+ subgroup compared to other subgroups. However, the limited number of patients enrolled in this subgroup (34 patients in Valchlor arm, 41 patients in control arm) contributes to the uncertainty of this estimate.

Table 27 Subgroup Analysis of CAILS Response

CAILS Response	Yaupon Arm	Control Arm	Response Ratio	95%CI
Overall	71/119 (60%)	59/123 (48%)	1.24	0.98, 1.58
Gender				
Male	40/71 (56%)	33/72 (46%)	1.23	0.89, 1.71
Female	31/48 (65%)	26/51 (51%)	1.27	0.90, 1.81
Age Group				
<64	56/85 (66%)	42/82 (51%)	1.29	0.99, 1.69
65+	15/34 (44%)	17/41 (41%)	1.06	0.64, 1.76
Duration of Disease				
< 6m	27/43 (63%)	22/42 (52%)	1.20	0.83, 1.76
6m to < 2y	17/30 (57%)	13/34 (38%)	1.48	0.89, 2.53
2y+	27/46 (59%)	24/47 (51%)	1.15	0.79, 1.68
Disease Stage at Randomization				
IA	40/65 (62%)	26/64 (41%)	1.51	1.08, 2.18
IB or IIA	31/54 (57%)	33/59 (55%)	1.03	0.74, 1.42

Table 28 Subgroup Analysis of SWAT Response

SWAT Response	Yaupon Arm	Control Arm	Response Ratio	95%CI
Overall	59/119 (50%)	57/123 (46%)	1.07	0.82, 1.39
Gender				
Male	34/71 (48%)	34/72 (47%)	1.01	0.72, 1.43
Female	25/48 (52%)	23/51 (45%)	1.15	0.77, 1.73
Age Group				
<64	47/85 (55%)	40/82 (49%)	1.13	0.85, 1.53
65+	12/34 (35%)	17/41 (41%)	0.85	0.47, 1.51
Duration of Disease				
< 6m	21/43 (49%)	21/42 (50%)	0.98	0.64, 1.50
6m to < 2y	16/30 (53%)	15/34 (44%)	1.21	0.73, 2.00
2y+	22/46 (48%)	21/47 (45%)	1.07	0.70, 1.65
Disease Stage at Randomization				
IA	29/65 (45%)	24/64 (38%)	1.19	0.80, 1.79
IB or IIA	30/54 (56%)	33/59 (56%)	0.99	0.71, 1.38

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Efficacy results for 2005NMMF-201-US support the proposed dosing for Valchlor for the treatment of Stage I MF-type CTCL.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to analysis of duration of response in Section 6.1.5 for a review of the persistence of efficacy.

6.1.10 Additional Efficacy Issues/Analyses

Pathology Analysis
All patients were required to have local and central pathology confirmation of the diagnosis of mycosis fungoides. Diagnosis confirmation was done through histological criteria (refer to Figure 2). Algorithm criteria (refer to Figure 3) was only done for patients who did not meet the diagnosis via histological criteria (15% of patients).

Two-hundred-five (85%) of 242 patients had MF pathology-confirmed diagnosis on both central and local review. Thirty-three (14%) patients required algorithm criteria for confirmation of diagnosis on both central and local pathology review. Four patients (2%) did not have both local and central pathology review. There were no patients who did not satisfy either local or central pathology criteria for MF diagnosis.

Table 29 Pathologic Confirmation of Mycosis Fungoides Diagnosis

Confirmation of Mycosis Fungoides Diagnosis	Central Pathology Review		
Local Pathology Review	Histological Criteria	Algorithm Criteria	Neither
Histological Criteria	205	4	1
Algorithm Criteria	10	19	0
Neither	2	1	0

Sensitivity analysis excluding the four patients without both local and central pathology confirmation did not change the conclusions for CAILS response (primary endpoint) and

SWAT response. Both endpoints would still have met the ratio criteria for non-inferiority (lower bound of 95% CI exceeds 0.75).

Table 30 Sensitivity Analysis for Pathology-Confirmed Population

Sensitivity Analysis	ITT population (N=242)	ITT population excluding patients without pathology confirmation (N=238)
CAILS response rate ratio (95%CI)	1.24 (0.98, 1.58)	1.25 (0.99, 1.59)
SWAT response rate ratio (95% CI)	1.07 (0.82, 1.39)	1.09 (0.84, 1.42)

Comparison to Published Literature

The results of this clinical trial are not consistent with those in published literature (Table 31). The reported CR rates in Stage I MF with topical NM therapy ranges from 60-80%. In this clinical trial, a comparable endpoint (SWAT response) showed CR rates of 7% in the Valchlor arm and 3% in active control arm. The overall SWAT response rate (CR+PR) was 50% in the Valchlor arm and 46% in the active control arm.

Reviewer Comment: Possible causes for the differences between the results of this clinical trial and published literature include trial design and methodology issues. The four clinical trials in Table 31 were single-arm clinical trials with inherent limitations of reporting bias. In addition, all but one of the four reference clinical trials were retrospective in design. None of the published trials on topical NM treatment for MF were randomized trials. Finally, the methods for assessing responses were not standardized as was done with this clinical trial.

Table 31 Comparison of Results of Study-201 to Published Literature

Reference	Description	Results
Vonderheid, 1989	**Design:** Retrospective analysis of medical records **Drug:** NM 0.01-0.02%, aqueous formulation	**CR rates:** St IA 80% (71/89), St IB 68% (45/66), St IIA 28/46 (61%) **Definition of CR:** complete disappearance of clinically detectable disease for at least 2 weeks and was confirmed in most cases by skin biopsy specimens
Ramsay, 1988	**Design:** Retrospective analysis of medical records **Drug:** NM 0.017% aqueous formulation	**CR Rates at 2 years:** St I 76% (48/63), St II 45% (20/44) **Definition of CR:** clearance of all lesions
Kim, 2003	**Design:** Retrospective analysis of medical records **Drug:** NM 0.01-0.02%, aqueous formulation (prior to 1980), ointment formulation (post 1980)	**Response Rates:** T1 disease (N=107): 65% CR (N=70), 28% PR (N=30), 93% CR+PR T2 disease (N=88): 34% CR (N=30), 38% PR (N=33), 72% CR+PR **Definition of Responses:** CR was defined as complete clinical regression of all MF lesions; PR, as any response less than complete but greater than 50% clinical improvement.
de Quatrebarbes, 2005	**Design:** Single arm prospective clinical trial **Drugs:** NM 0.02% aqueous formulation and betamethasone cream	**CR Rate:** St IA 61% (20/33), St IB 58% (15/26), St IIA 40% (2/5) **Definition of CR:** CR was defined as the disappearance of all clinical lesions of MF.
this review (NDA 202317)	**Design:** RCT, active control **Drugs:** Arm 1: NM 0.02% PG formulation Arm 2: NM 0.02% aquaphor formulation	**SWAT CR:** Arm 1 (N=119): CR 7%, CR+PR 50% Arm 2 (N=123): CR 3%, CR+PR 46%

Protocol Violations
Thirty nine (16%) of 242 patients had use of prohibited concomitant medications. Thirteen (5%) of 242 patients used topical corticosteroids, which the protocol permitted to be used on non-MF lesions. Documentation was provided that topical steroid use was confined to non-index lesions except for two patients: 013-001 and 012-021. Twenty-seven (11%) of 242 patients were prescribed short term steroids for concurrent or preexisting medical conditions. Routes of administration included eye drops, nasal sprays, inhalers, and injections as well as oral steroids. One patient (010-047) received concomitant UVB treatment 3 days prior to the last visit.

Sensitivity analysis excluding the 39 patients with use of prohibited concomitant treatments did not change the conclusions for CAILS response (primary endpoint) and SWAT response. Both endpoints would still have met the ratio criteria for non-inferiority (lower bound of 95% CI exceeds 0.75).

Table 32 Sensitivity Analysis Excluding Patients who Received Prohibited Concomitant Treatments

Sensitivity Analysis	ITT population (N=242)	ITT population excluding patients who received prohibited concomitant treatments (N=203)
CAILS response rate ratio (95%CI)	1.24 (0.98, 1.58)	1.23 (0.94, 1.62)
SWAT response rate ratio (95% CI)	1.07 (0.82, 1.39)	1.03 (0.76, 1.38)

Seventeen (7%) of 242 patients were reported to have other protocol deviations primarily consisting of missed visits or wrong or missing data.

Reviewer Comment: Overall, review of above protocol violations did not identify cause for lack of reliability of the efficacy and safety analysis. Major protocol violation involving randomization was discussed in Section 6.1.1.

7 Review of Safety

Safety Summary

The safety of Valchlor was evaluated in 255 patients with early stage mycosis fungoides in one randomized, active-control, observer-blinded clinical trial (Clinical Trial 2005NMMF-201-US). A summary of the key safety results from this clinical trial are listed below.

- Topical mechlorethamine was applied once daily. The duration of treatment was similar between treatment arms with a median of approximately 52 weeks. Fifty-five percent of patients required suspension of treatment or reduction of dose frequency during the clinical trial.

- Dermatitis is a known adverse event with topical mechlorethamine therapy. In this clinical trial, 73% in Valchlor arm and 69% in control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in Valchlor arm and 19% in control arm. Treatment discontinuations due to AEs (22% in Valchlor arm, 18% in control arm) were due to skin-related AEs. Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial.

- Eleven of 255 (4%) patients developed non-melanoma skin cancer (nMSC) during the course of the clinical trial or during long-term follow-up. Eight patients developed nMSC during treatment with topical mechlorethamine. Risk factors associated with development of nMSC include age $\geq$ 65 years and prior history of nMSC, but not duration of MF or treatment type (Valchlor vs. control formulation).

However, due to inadequate product quality characterization of clinical trial lots of Valchlor (refer to Section 4.1), the above safety results cannot be extrapolated to the proposed commercial product lots of Valchlor. Applicant will need to conduct one or more clinical trials to establish the safety of commercial product lots of Valchlor.

In addition, post-treatment safety follow-up in Study-201 is inadequate in duration to assess the long-term safety risks, including risk of development of secondary skin cancers. The median duration of documented follow-up post-treatment was 1 day post-treatment cessation in both treatment arms. Per protocol, 12 months of follow-up was recommended for all patients following cessation of treatment for any reason.

7.1 Methods

The safety of all patients enrolled in this study was monitored throughout the study. A physical exam and adverse event (AE) reporting was part of each clinic visit (monthly

for the first 6 months and every two months for the last 6 months). Patients were instructed to notify the study staff of any problems that occurred between visits and, if necessary, be evaluated by the Investigator or study staff at an unscheduled interim visit. Severity of adverse events and relationship to study medication were assessed by the investigator.

Blood specimens for serum chemistries (including sodium, chloride, bicarbonate, potassium, BUN, creatinine, glucose, SGOT (AST), SGPT (ALT), alkaline phosphate and total bilirubin, and CBC (RBCs, WBCs with differential, platelets, hematocrit, and hemoglobin) were obtained at baseline, month 1, 4, and 8, and at the last study visit (month 12).

During the 12 month treatment period, patients were evaluated at each clinic visit for dermatitis, the known toxicity associated with topical nitrogen mustard. The occurrence of skin cancer was also assessed at each clinic visit during the 12 month treatment period and for an additional 12 months after completing protocol therapy.

As discussed in Section 5.3.1.4, the safety population was defined as patients who had taken at least $\geq$ 1 dose of the study medication. The safety population was used as the basis for the analysis of laboratory and adverse event data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for Valchlor was performed by review of the following items submitted by the Applicant (Yaupon Therapeutics, Inc.):

- Summary of Clinical Safety
- Protocol and Statistical Analysis Plan for 2005NMMF-201-US
- Clinical study report for 2005NMMF-201-US
- Raw and derived datasets for 2005NMMF-201-US
- Case report forms for 2005NMMF-201-US
- Response to Information Requests
- Proposed labeling for Valchlor
- 120-day safety update report

7.1.2 Categorization of Adverse Events

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 8.1). Verbatim terms were provided. While the data were still blinded, medical personnel at Yaupon verified the MedDRA coding, and performed modified MedDRA coding shown side-by-side with standard MedDRA coding. Modified coding was performed by the Yaupon for the following reasons:

(1) to capture all terms related to “local dermal irritation” into “Skin and subcutaneous tissue disorders” SOC; standard MedDRA coding would have classified administration

site conditions into “General disorders” SOC and procedure complications (e.g., wound) into “Injury, poisoning and procedural complications” SOC

(2) to capture all terms related to neoplasms and reclassified as “Neoplasms malignant” and “Neoplasms benign(incl cysts and polyps)” SOC; standard MedDRA coding classified nodules and masses into the system-related SOC (e.g., breast nodule went into Reproductive SOC).

Reviewer Comment: Modified MedDRA recoding as performed by the Sponsor is acceptable because standard MedDRA coding was displayed side-by-side in the AE datasets which allowed for cross-checking of the recoding. However, the Sponsor’s referral to their modified MedDRA recoding as SMQ (Standardised MedDRA Query) coding is not acceptable as SMQ terminology refers to prespecified MedDRA grouping of related terms. AE tables displayed in this review are based standard MedDRA coding unless otherwise specified to allow comparisons or reference to this application review in the future.

AE severity was captured using the following criteria:

- **Mild**: Grade I NCI Common Toxicity; or if not found in the NCI Common Toxicity table, an adverse event that is asymptomatic or barely noticeable to the patient; not interfering with patient’s daily activity performance or functioning; generally not requiring alteration or cessation of study drug administration; and/or ordinarily not needing therapeutic intervention.
- **Moderate:** Grade II NCI Common Toxicity; or if not found in the NCI Common Toxicity table, an adverse event of sufficient severity as to possibly make the patient moderately uncomfortable; possibly influencing the patient’s daily activity performance or functioning; generally not impairing the patient’s ability to continue in the study; and/or possibly needing therapeutic intervention.
- **Moderately Severe:** Grade III NCI Common Toxicity; or if not found in the NCI Common Toxicity table, an adverse event generally causing severe discomfort; significantly influencing the patient’s daily activity performance or functioning; generally requiring alteration or cessation of study drug administration; and/or generally requiring therapeutic intervention.
- **Severe:** Grade IV NCI Common Toxicity; or if not found in the NCI Common Toxicity table, an adverse event that is considered to be life-threatening; resulting in significant disability or incapacity; and/or representing the worst possible occurrence of that event.

Reviewer Comment: According to the protocol, AE severity would be graded using Common Terminology Criteria for Adverse Events (CTCAE v3), and provided for additional details as listed above. The AE log pages in the case report forms do not indicate CTCAE v3, and list severity as 1=Mild, 2=Moderate, 3=Moderately Severe, and 4=Severe. Note that CTCAE v3 Grading system is as follows: Grade 1=Mild, Grade

2=Moderate, Grade 3=Severe, Grade 4=Life threatening or disabling AE, Grade 5=Death. Hence, the AE severity grading in this clinical trial may not be consistent with CTCAE v3.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable. The Applicant submitted only one clinical trial.

7.2 Adequacy of Safety Assessments

The data submitted to this NDA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by this reviewer. Verbatim AE terms were provided.

The Applicant did not provide adequate follow-up duration for the assessment of skin cancers post-treatment. The protocol recommended all patients to be followed for 12 months following cessation of treatment for any reason. Only 6 patients had follow-up ≥ 60 days post-treatment for monitoring for skin cancers. The median duration of follow-up for skin cancer monitoring was 1 day post-treatment cessation.

Inspections were conducted at three clinical sites and DSI findings include the following: Refer to Section 3.2 for the summary of DSI findings.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Demographics and Baseline Disease Characteristics of Safety Population
The safety population consisted of 255 patients (128-PG, 127-AP) who received ≥ 1 application of the study medication. The two groups showed similar distributions in gender, age group, and race.

Reviewer Comment: The safety population included patients treated at the NYU site, regardless of protocol violation involving randomization.

However, there were more patients in the Valchlor arm who had less disease extent compared to the control arm (Stage IA 59% in Valchlor versus 50% in control arm).

Table 33 Demographics and Baseline Disease Characteristics of Safety Population

Parameter		**PG (Yaupon) N = 128**	**AP (Control) N = 127**
Gender	Male	75 (59%)	76 (60%)
	Female	53 (41%)	51 (40%)
Age (years)	Mean (SD)	54.6 (14.3)	56.5 (14.3)
	Range	24 to 83	11 to 88
Groups	<18	0	1 (1%)
	18 to 39	26 (20%)	17 (13%)
	40 to 64	65 (51%)	67 (53%)
	≥ 65	37 (29%)	42 (33%)
Race	Caucasian	95 (74%)	93 (73%)
	African-American	16 (13%)	19 (15%)
	Asian	4 (3%)	3 (2%)
	Other	13 (10%)	12 (10%)
Stage, at randomization, N(%)			
IA		75 (59%)	63 (50%)
IB		51 (40%)	62 (49%)
IIA		2 (2%)	2 (2%)
%BSA, at baseline			
Mean (SD)		12.0 (11.8)	16.6 (17.2)
Median (Range)		8 (1 to 61)	10 (1 to 90)
Groups	1% to 9%	74 (58%)	63 (50%)
	≥ 10%	54 (42%)	64 (50%)

Exposure
The median and mean duration of treatment were similar between the two groups. However, there were more patients in the PG arm who required treatment suspension or reduction in dose frequency (60% vs. 50%).

Table 34 Exposure Duration in Weeks

Exposure Duration in Weeks	**PG (Yaupon) N=128**	**AP (Control) N=127**
Mean (SD)	39.2 (19.3)	41.9 (17.4)
Median	51.7	52.0
Range	1.3 to 59.9	1.6 to 58.0
By Range of Weeks, n (%)		
Missing	2 (2%)	2 (2%)
0	0	0
>0 to <2	2 (2%)	1 (1%)
2 to <4	2 (2%)	2 (2%)
4 to <12	21 (16%)	10 (8%)
12 to <24	8 (6%)	13 (10%)
24 to <48	13 (10%)	14 (11%)
≥ 48	80 (63%)	85 (67%)

Table 35 Number of Patients With Treatment Modifications

Treatment Modification	**PG (Yaupon) N=128**	**AP (Control) N=127**
Treatment Suspension		
Any	54 (42%)	44 (35%)
Duration of Suspension ≥ 7 days	48 (38%)	29 (23%)
Duration of Suspension ≥ 14 days	30 (23%)	15 (12%)
Reduction in Dose Frequency		
Any	54 (42%)	35 (28%)
Every other day	27 (21%)	17 (13%)
Every three days	20 (16%)	3 (2%)
Other	27 (21%)	24 (19%)
Any Treatment Suspension or Reduction in Dose Frequency	77 (60%)	64 (50%)

The daily drug substance (DS) use estimates appeared to be slightly higher for the AP arm than the PG arm. However, this difference was probably due to greater number of patients with less BSA involvement in the PG arm. Daily DS use estimates analyzed per BSA subgroup (<10% versus ≥ 10%) showed similar figures between treatment arms.

Table 36 Daily Use Estimates (Drug Substance in Milligrams per Day)

Daily Use Estimates (drug substance in milligrams per day)	**PG (Yaupon) N=128**	**AP (Control) N=127**
All Safety Population with non-missing values	N=124	N=125
Average daily use		
Mean (SD)	0.58 (0.50)	0.69 (0.50)
Median	0.41	0.57
Range	0.05 to 3.33	0.10 to 3.41
95% quantile	1.54	1.51
97.5% quantile	1.81	1.81
All Safety Population, baseline BSA<10%	N=72	N=62
Average daily use		
Mean (SD)	0.36 (0.30)	0.45 (0.30)
Median	0.27	0.32
Range	0.05 to 1.81	0.10 to 1.31
95% quantile	1.07	1.05
97.5% quantile	1.35	1.26
All Safety Population, baseline BSA ≥ 10%	N=52	N=63
Average daily use		
Mean (SD)	0.88 (0.56)	0.93 (0.55)
Median	0.83	0.80
Range	0.10 to 3.33	0.24 to 3.41
95% quantile	1.90	1.80
97.5% quantile	2.93	2.95

Reviewer Comment: The approved dose for IV mechlorethamine is 0.4 mg/kg (divided to 0.1 to 0.2 mg/kg per day). However, the most common use of IV mechlorethamine would be as a component of Hodgkin lymphoma regimens. Unlabeled dosing for IV mechlorethamine in MOPP is 6 mg/m^2 on days 1 and 8 of a 28-day cycle. In the Stanford V regimen (also unlabeled dosing for mechlorethamine), the IV mechlorethamine dose is 6 mg/m^2 on day 1 of a 28-day cycle (total of 3 cycles). A

6 mg/m^2 dose of mechlorethamine would correspond to dose of 10.4 mg for a BSA of 1.73 mg/m^2. Hence, although the amount of mechlorethamine administered IV at a single timepoint is higher, because of the duration of exposure, the exposure to topical mechlorethamine would be higher than average IV dosing regimens on a milligram-per-milligram basis over time.

7.2.2 Explorations for Dose Response

The Applicant did not examine different doses of topical Valchlor in clinical trial 2005NMMF-201-US. All patients were started at an initial dose of once daily. Although 54 of 128 patients treated with Valchlor subsequently received lower frequency, this was a protocol-directed reduction. Therefore, an exploration of dose-response for safety could not be performed.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology-Toxicology review for details.

7.2.4 Routine Clinical Testing

Refer to Sections 7.4.2 to 7.4.4.

Routine clinical assessments in 2005NMMF-201-US include medical history, physical exam, and laboratory tests (CBC, chemistry panel). History and physical exams were conducted every 4 weeks to month 6, then every 8 weeks to month 12. Laboratory tests were conducted at baseline and at months 1, 4, 8, and 12. Clinical documentation of skin cancers (type and location) was performed every 3 months for an additional 12 months for all patients who receive at least one dose of study drug.

Refer to Section 5.3.1.4 for detailed schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable. Valchlor is not systemically absorbed. Refer to Clinical Pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Mechlorethamine is an antineoplastic alkylating agent. Known class effects of intravenous alkylating agents include myelosuppression, nausea, vomiting, hypersensitivity reactions, infertility, and secondary malignancies. In addition, mechlorethamine is also an irritant and may cause thrombophlebitis. Extravasation of mechlorethamine into subcutaneous tissues result in painful inflammation. The

mechlorethamine label (i.e., Mustargen label) recommends avoidance of contact with mucosal membranes, especially those of the eyes.

Reviewer Comment: As topical mechlorethamine is not systemically absorbed (refer to clinical pharmacology review), the risks associated with systemic exposure such as myelosuppression, nausea, vomiting, infertility are mitigated. However, local toxicity with topical application remains as a safety issue. Regarding secondary malignancies, the risk of secondary skin malignancies remains as a safety issue.

7.3 Major Safety Results

Table 37 Safety Summary

Safety Summary	PG (Yaupon) N=128	AP (Control) N=127
Deaths	1 (1%)	0
Serious AE	14 (11%)	11 (9%)
Discontinued Treatment due to AE	28 (22%)	23 (18%)
Any Grade 3 to 4 AE	47 (37%)	34 (27%)
Any AE	108 (84%)	115 (91%)

7.3.1 Deaths

One patient, 011-0001 on the PG arm, died from widely disseminated metastatic colorectal cancer after <2 months on treatment. The patient initiated treatment on April 17, 2008. The last clinic visit was on May 16, 2008. On (b) (6) the patient underwent an MRI for severe back pain. The MRI revealed widely disseminated carcinoma (biopsy results favored colon primary). The patient entered hospice care on (b) (6) and died (b) (6)

Reviewer Comment: The event of secondary malignancy (widely disseminated colorectal cancer) in this patient is unlikely to be related to topical mechlorethamine exposure. Topical mechlorethamine is not systemically absorbed. Also, the <2 month interval from alkylating agent exposure to development of widely metastatic cancer is also not consistent with known long lag times for secondary malignancies.

7.3.2 Nonfatal Serious Adverse Events

Twenty-six patients (14-PG; 11-AP) experienced an SAE while on this study. The incidence categorized by SOC and Preferred Term is shown in Table 38.

Table 38 Serious Adverse Events in ≥ 2% of the Safety Population

MedDRA Preferred Term	PG (Yaupon) N=128	AP (Control) N=127
Any SAE	14 (11%)	11 (9%)
Cardiac failure congestive	–	2 (2%)
Myocardial infarction	–	2 (2%)
Pneumonia	2 (2%)	–

In the PG (Yaupon) treatment arm, SAEs not listed in Table 38 include (1 patient each): G4 cerebrovascular accident, G4 asthma, G3 peripheral vascular disorder, G3 parathyroidectomy, G3 menorrhagia, G3 appendicitis, G3 aortic aneurysm, G2 thyroid gland cancer, G2 staphylococcal infection, G2 pain, G2 haemorrhoids, G2 chest discomfort, G2 atrial fibrillation, and G1 global amnesia.

In the AP(control) treatment arm, SAEs not listed in Table 38 include (1 patient each): G4 neuroendocrine carcinoma of the skin, G4 gastrointestinal infection, G4 cellulitis, G4 dizziness, G3 lung disorder (verbatim term: “Pulmonary condition progression–lung biopsy required”), G2 pancreatitis, and G2 biliary colic.

None of the SAEs were considered related to study treatment by the investigators.

7.3.3 Dropouts and/or Discontinuations

Skin-related AEs were the cause for treatment discontinuations due to AEs (22% in Valchlor arm, 18% in control arm).

The median time to discontinuation due to AEs was 1.7 months (95%CI: 1.2, 2.4) in the Valchlor arm and 2.8 months (95% CI: 1.4, 3.8) in the AP control arm.

Reviewer Comment: Time to discontinuation due to AEs was estimated based on Kaplan-Meier method. Reference time points are start date of therapy to date of last treatment application.

Table 39 Adverse Events Leading to Treatment Discontinuation

AEs Leading to Treatment Discontinuation	PG (Yaupon) N=128		AP (Control) N=127	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All Treatment Discontinuations	22%	18%	18%	13%
Treatment Discontinuation due to Skin-related AE	22%	18%	18%	13%
Skin irritation (a)	18%	14%	16%	12%
Pruritus (b)	2%	2%	2%	1%
Blister or skin ulcer (c)	2%	2%	1%	1%
Bacterial skin infection (d)	2%	2%	–	–
Squamous cell carcinoma	1%	1%	–	–
Chest discomfort	1%	–	–	–

(a) Includes dermatitis contact, drug hypersensitivity, edema, erythema, hypersensitivity, pain of skin, rash pruritic, rash vesicular, skin burning sensation, skin disorder, skin irritation, urticaria, urticaria contact

(b) Includes pruritus, generalized pruritus

(c) Includes blister, skin ulcer, allergic reaction-blister, wound

(d) Includes blister infected, cellulitis, folliculitis, furuncle, impetigo, rash pustular, staphylococcal abscess, staphylococcal infection, wound infection

Reviewer Comments:
1. Patient 12-021 who discontinued due to chest discomfort also had concomitant infected blister listed as a reason for discontinuation of therapy due to AE.
2. Patient 02-045 discontinued treatment due to squamous cell carcinoma (SCC) because this patient required initiation of systemic therapy for SCC.

7.3.4 Significant Adverse Events

Dermatitis
Dermatitis is a known adverse event with topical mechlorethamine therapy. In this clinical trial, 73% in Valchlor arm and 69% in control arm experienced dermatitis, or a complication from dermatitis. Grade 3-4 dermatitis was reported in 29% of patients in Valchlor arm and 19% in control arm (refer to Table 40).

Treatment discontinuations due to AEs (22% in Valchlor arm, 18% in control arm) were due to skin-related AEs, predominantly due to dermatitis (refer to Table 39). Most cases of dermatitis resolved, however 9% in Valchlor arm and 13% in control arm had residual dermatitis at the end of the clinical trial (refer to Table 41).

Table 40 Dermatitis Adverse Events

Dermatitis AE Terms	PG (Yaupon) N=128		AP (Control) N=127	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin irritation (a)	58%	23%	58%	17%
Bacterial skin infection (b)	11%	2%	9%	2%
Blister or skin ulcer (c)	6%	3%	4%	1%
Pruritus (d)	20%	4%	17%	2%
Skin hyperpigmentation (e)	5%	–	7%	–
Any of the above (a to e)	73%	29%	69%	19%

(a) Includes actinic keratosis, application site irritation, dermatitis, dermatitis contact, dermatitis psoriasiform, drug hypersensitivity, dry skin, eczema, erythema, flank irritation, generalized erythema, hyperkeratosis, hypersensitivity, intertrigo, neurodermatitis, pain of skin, rash, rash erythematous, rash papular, rash pruritic, rash vesicular, skin burning sensation, skin erosion, skin fissures, skin irritation, skin warm, urticaria, urticaria contact

(b) Includes blister infected, cellulitis, folliculitis, furuncle, impetigo, rash pustular, staphylococcal abscess, staphylococcal infection, wound infection

(c) Includes blister, skin ulcer, allergic reaction-blister, wound

(d) Includes pruritus, generalized pruritus

(e) Includes skin hyperpigmentation

Table 41 Reversibility of Adverse Events

Dermatitis AE Terms	PG (Yaupon) N=128		AP (Control) N=127	
	% with AE	% with unresolved AE	% with AE	% with unresolved AE
Skin irritation (a)	58%	6%	58%	9%
Bacterial skin infection (b)	11%	2%	9%	3%
Blister or skin ulcer (c)	6%	2%	4%	–
Pruritus (d)	20%	–	17%	2%
Any of above (a to d)	71%	9%	67%	13%

(a) Includes actinic keratosis, application site irritation, dermatitis, dermatitis contact, dermatitis psoriasiform, drug hypersensitivity, dry skin, eczema, erythema, flank irritation, generalized erythema, hyperkeratosis, hypersensitivity, intertrigo, neurodermatitis, pain of skin, rash, rash erythematous, rash papular, rash pruritic, rash vesicular, skin burning sensation, skin erosion, skin fissures, skin irritation, skin warm, urticaria, urticaria contact

(b) Includes blister infected, cellulitis, folliculitis, furuncle, impetigo, rash pustular, staphylococcal abscess, staphylococcal infection, wound infection

(c) Includes blister, skin ulcer, allergic reaction-blister, wound

(d) Includes pruritus, generalized pruritus

Reviewer Comment: The frequency of dermatitis reported in this clinical trial (70% with Valchlor arm, 67% with control arm) is consistent with published estimates of dermatitis of 50-70% with topical mechlorethamine therapy.

Non-melanoma skin cancer

A total of eleven patients (refer to Table 42) developed a non-melanoma skin cancer within one year of ending treatment in Study 201. Eight of these occurred during treatment and 3 occurred during the one-year follow-up period. However, only one patient discontinued treatment due to development of skin cancer.

Three of these patients had been treated with Valchlor 0.02%, 7 had been treated with control formulation, and 1 patient had been treated with control formulation for 12 months followed by 6 months of Valchlor 0.02% for 7 months in Study 202.

The histology of the skin cancers include: SCC only (3 patients), BCC only (5 patients), SCC and BCC (2 patients), and Merkle cell carcinoma (1 patient). Three patients had multiple skin cancers.

Subgroup analysis was performed to identify populations at higher risk for development of skin cancer. As expected, patients older than 65 or with a prior history of non-melanoma skin cancer were at higher risk (RR 5.9 for age $\geq$ 65 compared to age <65; and RR 18.6 for prior history of skin cancer vs no prior history). Treatment type (Valchlor vs. control) and duration of MF ($\geq$ 1 year vs < 1 year) showed no differences in risks for development of skin cancer.

Reviewer Comment: The frequency of skin cancer (non-melanoma) reported in this clinical trial (11/255 patients, 4% [95%CI 2%;8%]) is consistent with published reports of skin cancer with topical mechlorethamine therapy. Kim et al, reported an skin cancer incidence of 8 in 203 (4%) patients treated with topical mechlorethamine as initial therapy for MF; this was a long-term follow-up report published in 2003 based on patients treated with topical mechlorethamine from 1968 to 1999. Vonderheid et al. reported 25 patients (8%) who developed SCC and 21 patients (6%) who developed BCC in 331 patients treated with topical mechlorethamine therapy; this was a long-term follow-up report published in 1984 based on patients treated with topical mechlorethamine from 1968 to 1982.

The Applicant did not provide adequate follow-up duration for the assessment of skin cancers post-treatment. The protocol recommended all patients to be followed for 12 months following cessation of treatment for any reason. Only 2 patients had follow-up >90 days post-treatment for monitoring for skin cancers. The median duration of documented follow-up for skin cancer monitoring was 1 day post-treatment cessation.

Table 42 Patients with Non-Melanoma Skin Cancers

Patient ID	Age/ Gender	Treatment Arm [Duration of Therapy, months]	AE Term	Months post-start of therapy	Treated Area?	Prior Dermatologic History	Duration of MF (years)
02-026	67/F	AP (0.02%) [12m] PG (0.04%) [7m]	Superficial BCC, L shoulder	28	N	None	<1
02-042	52/M	PG [5m]	BCC, post auricular region	1 day	N	BCC, 13 yrs prior	12
02-045	66/M	PG [8m]	SCCA, frontal scalp	1.5	N	BCC, 8 yrs prior	11
			BCC, R upper chest	5	Y		
			SCCA, scalp	5	N		
			SCCA, forehead	6	N		
			Metastatic SCCA, R temple	2 months prior	N		
			Metastatic SCCA, above R ear	0.8	N		
02-064	67/F	PG [6m]	SCCA, R upper back	21	Y	BCC, 1 yr prior cSCCA, 2 yrs prior	10
02-072	74/M	AP [12m]	SCCA, L temple	6	N	BCC, no date	<1
			BCC, chin	12	N		
03-005	41/M	AP [12m]	BCC, R post lat calf	9	Unk	BCC, 1 yr prior	<1
05-024	57/F	AP [12m]	BCC, forehead	5 months prior	N	Non-melanoma skin cancer, 39 yrs prior	<1
			BCC, L lat thigh	2	Y		
			BCC, L upper shoulder	3	Y		
			BCC, R lower leg	23	Y		
09-010	64/M	AP [12m]	SCCA, R cheek	4	N	BCC, 2 yrs prior	4
10-022	88/F	AP [6m]	Merkle cell CA, R thigh	2	N	None	24
10-049	60/M	AP [12m]	BCC, above R ankle	8	Y	BCC, 9 yrs prior SCCA, 9 yrs prior	<1
11-013	82/M	AP [4m]	SCCA, dorsal L hand	7	Unk	Dermal lesions removed, <1 yr prior	<1

Section 8.4 (Follow-up Visit) of the protocol (original version, date 1/6/06) states recommended follow-up duration:

> "All patients who enter the study and receive at least one dose of study drug, regardless of the reason for withdrawal or study termination, will, if at all possible, have a follow-up evaluation at least eight (8) weeks following their last application of NM ointment. Patients who complete the 12 month study will be followed for an additional twelve months, to capture additional safety data where possible. Follow-up visits every three (3) months will consist of a targeted history and physical exam and toxicity recordation with specific attention to squamous cell carcinoma of the skin."

Section 8.4 (Post-Treatment Follow-Up Visit) of the protocol was amended on 3/13/08 to the following:

> "The FDA has requested that all patients who enter the study and receive at least one dose of study drug, regardless of the reason for withdrawal or study termination, or if they complete the twelve (12) month study, will, if at all possible, be followed for an additional twelve (12) months to capture additional safety data. Follow-up visits every three (3) months will consist of a targeted history (including any ongoing AEs), current treatments for NM and toxicity recordation with specific attention to squamous cell carcinoma of the skin."

Reviewer Comment (1): Development of secondary malignancies is a known complication of alkylating agent therapy. Because of the lag time to development of secondary malignancies, extended follow-up following completion of treatment is needed to adequately the assess of secondary malignancies. For this clinical trial, the applicant failed to capture sufficient information as recommended in the protocol.

Reviewer Comment (2): At the reference date of 3/13/08 (protocol amendment #5), 185 out of 255 patients (73%) in the safety population were still receiving treatment, and should have been followed up for an additional 12 months to capture safety data.

According to the 120-day safety update submitted on 2 December 2011 (SDN 11):

> "Of the 255 patients treated, 223 (87.5%) had at least one follow-up visit scheduled on or around 90 days after completion of the first trial and 183 (71.8%) had a follow-up visit that occurred >300 days after stopping treatment with either formulation of mechlorethamine HCl (MCH) 0.02%. Included in the 223-patient cohort are the 98 patients who received at least one dose of mechlorethamine HCl gel 0.04% on Study 202. Eighty-two (83.7%) of these 98 patients were included in the cohort of 183 patients who had a follow-up visit >300 days after completing Study 201".

Reviewer Comment: This reviewer cannot verify the applicant's results in the above paragraph. The applicant's results are not supported by the relevant datasets (EX and

DF; exposure and disorder findings. The review team requested for the above information on 3 November 2011 and 11 January 2012.

According to clinical information submitted in SDN 18 (received 23 January 2012),

> "There have been no changes or additions to the data described in the 120-day safety update (Amendment 010, submitted 22 NOV 2011). The one year post treatment follow-up database was locked on 20 DEC 2011. No new skin cancers were reported between the date data were summarized for FDA in Amendment 010 and the time the database was locked."

Reviewer Comment: Applicant has not provided additional data as requested by the Agency regarding post-treatment follow-up for skin cancer. Analysis results as shown in Table 43 indicate inadequate follow-up of the patients post-treatment.

Table 43 Post-Treatment Follow-up for Non-Melanoma Skin Cancer

Post-Treatment Follow-up for Skin Cancer	PG (Yaupon) N=128	AP (Control) N=127
Number of patients who developed skin cancer	3	8
Duration of post-treatment follow-up for skin cancer in patients who did not develop skin cancer		
Median duration of post-treatment follow-up	1 day	1 day
Number of patients who did not develop skin cancer	125	119
Distribution		
Missing	3 (3%)	2 (2%)
Less than or equal to 1 day	84 (71%)	78 (66%)
2 to 30 days	30 (25%)	31 (26%)
31 to 60 days	5 (4%)	5 (4%)
61 to 180 days	3 (3%)	2 (2%)
181 to 360 days	0	1 (1%)
More than 360 days	0	0

7.3.5 Submission Specific Primary Safety Concerns

Refer to Section 7.3.4.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Refer to Section 7.3.4 for discussion of common cutaneous adverse events.

The only non-cutaneous adverse event occurring in ≥ 5% of patients was upper respiratory tract infection (9% Valchlor, 8% control arm). None of the upper respiratory tract infections were Grade 3 or 4 in severity.

7.4.2 Laboratory Findings

Table 44 Abnormal Laboratory Findings

Abnormal Laboratory Results	PG (Yaupon) N=128		AP (Control) N=127	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematology				
Hemoglobin Decreased	16%	–	18%	1%
Leukocyte count Decreased	7%	–	3%	–
Neutrophil count Decreased	5%	1%	8%	–
Lymphocyte count Decreased	20%	2%	17%	1%
Platelet count Decreased	2%	1%	3%	–
Basic Metabolic Panel				
Glucose Increased	39%	2%	35%	2%
Glucose Decreased	19%	1%	20%	–
Creatinine Increased	14%	–	15%	–
Bicarbonate Decreased	10%	–	9%	–
Potassium Decreased	7%	–	8%	1%
Potassium Increased	5%	–	6%	–
Sodium Decreased	2%	–	4%	–
Sodium Increased	3%	–	1%	–
Liver Function Panel				
ALT (SGPT) Increased	15%	–	18%	–
AST (SGOT) Increased	13%	–	15%	–
Alkaline phosphatase Increased	7%	–	6%	–
Total bilirubin Increased	3%	–	6%	–

The protocol required laboratory tests to be done at baseline, month 1, 4, 8, and at the last study visit (month 12). Local laboratories were used. Approximately 90% of the patients in the safety population had laboratory tests done on at least ≥ 3 visits. CTCAE v3 was used for grading of laboratory test abnormalities.

The following patients had a grade 3 or grade 4 hematology value:

- Patient 02-042 (PG arm): Grade 4 platelet count: Patient had a history of follicular lymphoma, and received several chemotherapy regimens including CHOP+Bleomycin+interferon, MINE, and ESHAP. Patient also had an autologous stem cell transplant in 1994. Patient was diagnosed with MDS 4 months after starting treatment on Study-201. The investigator assessed myelodysplastic syndrome (MDS) to be not related to NM. MDS was most likely a result of prior exposure to alkylating agents received for treatment for NHL.

- Patient 10-011 (PG arm): As shown below, grade 3 neutropenia was observed during the trial. One year prior to initiating this trial, patient's WBC was 3.1 with 31% neutrophils. Patient was African-American in descent.

Visit	WBC	ANC	CTCAE
1 year prior	3100//µL	960/µL	Grade 3
Baseline	4300/µL	2000/µL	
Month 1	3100/µL	960/µL	Grade 3
Month 4	4400/µL	2400//µL	
Month 8	3300/µL	990/µL	Grade 3
Final	3100/µL	930/µL	Grade 3

- Patient 02-063 (AP arm) had grade 3 anemia. This patient had iron deficiency anemia prior to entering the trial. He was treated with iron supplements and blood transfusions, but anemia recurred. Patient was then treated with IV iron infusions which stabilized his anemia. Colonoscopy and bone marrow evaluation were conducted, but the cause of patient's anemia has not been determined.

Three patients (2 PG and 1 AP) had a grade 3 lymphopenia during the trial:

- Patient 02-011 (PG arm): Grade 3 lymphopenia was observed 3 months after the initiation of topical NM (WBC=8100/µL; lymphocytes 3.3%, neutrophils 94.5%). This coincided with the diagnosis of active inflammatory bowel disease (IBD); the patient was withdrawn from the trial because corticosteroids were required to treat IBD.

- Patient 02-045 (PG arm): Grade 3 lymphopenia was reported at the final visit (WBC 5800/µL; lymphocytes=7.4%, neutrophils=80%). This patient was

withdrawn from the trial due to metastatic SCC; treatment had been initiated with Xeloda one month prior to the final blood draw.

- Patient 02-038 (AP arm): Grade 3 lymphopenia was reported at the month 1 visit (WBC 8100/µL; 5% lymphocytes, 5% eosinophils, neutrophils = 81%). This pattern of low lymphocytes, and elevated eosinophils and neutrophils persisted throughout the trial.

Four patients (2 patients on each treatment arm) had grade 3 hyperglycemia. All of these patients were diabetic.

One patient had grade 3 hypoglycemia at her final visit, glucose = 39 mg/dL. The investigator stated "Patient is not diabetic, never had low blood sugar, and had her sugar checked last week–it was 110 mg/dL, so 39 is most probably a lab error."

Grade 3 hypokalemia occurred in one patient. Patient was on hydrochlorothiazide for hypertension. When grade 3 hypokalemia was noted, patient was started on potassium supplements.

Reviewer Comment: There was no consistent pattern of change for the measured laboratory values. Patients who experienced ≥ grade 3 anemia, neutropenia, or thrombocytopenia were few (1-2%) and had alternative explanations to their cytopenia. The topical doses of mechlorethamine administered in this trial would have exceeded typical systemic doses of IV mechlorethamine on a per-cycle basis. Thus, the absence of severe cytopenias support the lack of systemic absorption of topical mechlorethamine.

7.4.3 Vital Signs

Vital signs were not collected in this clinical trial.

Reviewer Comment: Although the lack of systemic absorption of Valchlor makes it unlikely to observe changes in vital signs, changes mediated by local toxicity of Valchlor can induce changes in vital signs. However, the vital signs measurements are unlikely to be a sensitive assessment of systemic reactions to local toxicities and would not have likely contributed meaningful clinical information in the assessments of local toxicities.

7.4.4 Electrocardiograms (ECGs)

ECGs were not collected in this clinical trial. ECG changes are not expected with Valchlor due to the lack of systemic absorption of this topical formulation.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for AEs is not evaluable because the clinical trial did not examine different dose regimens for Valchlor in Study-201.

7.5.2 Time Dependency for Adverse Events

The median time to development of dermatitis was 1.4 months (95%CI: 1.1, 1.8) in the Valchlor arm and 1.8 months (95% CI: 1.6, 2.2) in the AP control arm. Dermatitis includes items (a-d) in Table 40: skin irritation, bacterial skin infection, pruritus, blister, or skin ulcer.

Reviewer Comment: Time to development of dermatitis AE was estimated based on Kaplan-Meier method. Reference time points were the start date of therapy to the date of onset of the dermatitis AE.

7.5.3 Drug-Demographic Interactions

Interpretation of drug-demographic interaction for analysis of adverse events is limited by the small size of the subpopulations, which contributes to the uncertainty of the estimates. The frequency of dermatitis (all grades and $\geq$ grade 3) did not consistently identify a subpopulation of patients (by gender, age, race) at increased risk for these adverse events. Subgroup analysis for occurrence of non-melanoma skin cancer is discussed in Section 7.3.4.

7.5.4 Drug-Disease Interactions

Because topical mechlorethamine is not absorbed systemically, drug-disease interaction analysis is not applicable for this application.

7.5.5 Drug-Drug Interactions

Systemic drug-drug interactions are not applicable for this application.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Mechlorethamine is a known carcinogen. Refer to Section 7.3.4 for discussion on occurrence of skin cancers in patients treated with topical mechlorethamine.

7.6.2 Human Reproduction and Pregnancy Data

Although the protocol required that men and women of child bearing potential use effective contraception, the wife of one of the participating subjects (003-0032-AP) became pregnant between 1 and 2 months after the subject initiated treatment. The pediatrician provided a letter documenting that the baby was carried to term (38 weeks) and was healthy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of Valchlor have not been established in the pediatric population. Clinical trial 2005NMMF-201-US enrolled one patient who was less than 18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The toxicities (i.e., dermatitis and/or secondary skin cancers) associated with Valchlor make it unlikely that this drug will be abused.

7.7 Additional Submissions / Safety Issues

The applicant submitted the 120-day safety update on 22 November 2011. Analysis of updated safety data from clinical trial 2005NMMF-201-US was integrated in Sections 7.2-7.6.

The applicant submitted additional safety analysis on 17 January 2012. The applicant claims that clinical data in Study-201 is helpful in comparing the (b) (4) and UIP products in the Valchlor treatment arm. Fourteen patients received treatment with UIP product during the conduct of Study-201.

Clinical Reviewer Comment: Safety information generated during the period of UIP treatment is confounded by prior (b) (4) treatment. Safety data of patients treated with UIP

product cannot be compared to patients treated with (b) (4) product due to carryover effect from prior (b) (4) treatment. In addition, exposure data in 14 patients treated with UIP product indicate that majority of treatment exposure in these 14 patients was from (b) (4) product (percentage of UIP treatment of total treatment duration, range 9% to 43%).

8 Postmarket Experience

Valchlor is not marketed in the United States.

9 Appendices

9.1 Literature Review/References

1. Remission of lesions in mycosis fungoides following topical application of nitrogen mustard. By John R. Haserick, Joseph H. Richardson, and Douglas J. Grant. Cleve Clin Q. 1983;50(2):91-5.

2. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood. 2009;113(21):5064-73.

3. de Quatrebarbes J, Estève E, Bagot M, Bernard P, Beylot-Barry M, Delaunay M, et al. Treatment of early-stage mycosis fungoides with twice-weekly applications of mechlorethamine and topical corticosteroids: a prospective study. Arch Dermatol. 2005;141(9):1117-20.

4. Duvic M, Olsen EA, Omura GA, Maize JC, Vonderheid EC, Elmets CA, et al. A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol. 2001;44(6):940-7.

5. Estève E, Bagot M, Joly P, Souteyrand P, Beylot-Barry M, Vaillant L, et al. A prospective study of cutaneous intolerance to topical mechlorethamine therapy in patients with cutaneous T-cell lymphomas. French Study Group of Cutaneous Lymphomas. Arch Dermatol. 1999;135(11):1349-53.

6. Farber EM, Schneidman HM, Llerena J. The natural history of mycosis fungoides. Calif Med. 1957;87(4):225-30.

7. Hamminga B, Noordijk EM, van Vloten WA. Treatment of mycosis fungoides: total-skin electron-beam irradiation vs topical mechlorethamine therapy. Arch Dermatol. 1982;118(3):150-3.

8. Hamminga L, Hermans J, Noordijk EM, Meijer CJ, Scheffer E, Van Vloten WA. Cutaneous T-cell lymphoma: clinicopathological relationships, therapy and survival in

ninety-two patients. Br J Dermatol. 1982;107(2):145-55.

9. Hoppe RT, Abel EA, Deneau DG, Price NM. Mycosis fungoides: management with topical nitrogen mustard. J Clin Oncol. 1987;5(11):1796-803.

10. Kim YH. Management with topical nitrogen mustard in mycosis fungoides. Dermatol Ther. 2003;16(4):288-98.

11. Kim YH, Chow S, Varghese A, Hoppe RT. Clinical characteristics and long-term outcome of patients with generalized patch and/or plaque (T2) mycosis fungoides. Arch Dermatol. 1999;135(1):26-32.

12. Kim YH, Jensen RA, Watanabe GL, Varghese A, Hoppe RT. Clinical stage IA (limited patch and plaque) mycosis fungoides. A long-term outcome analysis. Arch Dermatol. 1996;132(11):1309-13.

13. Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. Arch Dermatol. 2003;139(2):165-73.

14. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

15. Nam J-M. Confidence Limits for the Ratio of Two Binomial Proportions Based on Likelihood Scores: Non-Iterative Method. Biometrical Journal. 1995;37(3):375-9.

16. Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011;29(18):2598-607.

17. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53(6):1053-63.

18. Ramsay DL, Halperin PS, Zeleniuch-Jacquotte A. Topical mechlorethamine therapy for early stage mycosis fungoides. J Am Acad Dermatol. 1988;19(4):684-91.

19. Ramsay DL, Meller JA, Zackheim HS. Topical treatment of early cutaneous T-cell lymphoma. Hematol Oncol Clin North Am. 1995;9(5):1031-56.

20. Swerdlow SH, International Agency for Research on Cancer., World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008. 439 p. p.

21. Vonderheid EC, Tan ET, Kantor AF, Shrager L, Micaily B, Van Scott EJ. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol. 1989;20(3):416-28.

22. Watson JI, Wilkinson RD, Craig GE. Topical nitrogen mustard in cutaneous lymphosarcoma (mycosis fungoides). Can Med Assoc J. 1962;87:1284-5.

9.2 Labeling Recommendations

Labeling could not be generated for this application due to CMC deficiencies that lead to non-interpretability of efficacy and safety findings from Study-201, the primary basis for this application.

9.3 Advisory Committee Meeting

This application was not taken to Oncologic Drugs Advisory Committee.

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

/s/

ROMEO A DE CLARO
03/28/2012

ALBERT B DEISSEROTH
04/11/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202-317 **Applicant: Yaupon Therapeutics, Inc.** **Stamp Date: 07/27/2011**

Drug Name: Mechlorethamine Hydrochloride Gel 0.02% **NDA Type: 505(b)(2)**

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			REMS
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)2 mechlorethamine HCl (aka MCH, nitrogen mustard, NM), the same active substance contained in Mustargen@ (NDA#6695)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1Phase II Pivotal Trial to Evaluate the Safety and Efficacy of Nitrogen Mustard (NM) 0.02% Oinment Formulations in Patients with Stage I or IIA Mycosis Fungoides (MF) (protocol 2005NMMMF-201-US) Indication: 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) Pivotal Study #2 N/A Indication:	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		All US patients
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			100 patients followed for 1 year
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		No foreign sites
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

N/A

Reviewing Medical Officer — Date
Robert M. White, Jr., MD, FACP

Clinical Team Leader — Date
John R. Johnson, MD

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

/s/

ROBERT M WHITE
09/07/2011

JOHN R JOHNSON
09/07/2011