CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210308Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115577

MEETING MINUTES

Churchill Pharma
Attention: Paul Nemeth, Ph.D.
Vice President, Clinical Development and Regulatory Affairs
Churchill Pharmaceuticals, LLC
3602 Horizon Drive, Suite 160
King of Prussia, PA 19406

Dear Dr. Nemeth:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SoluMatrix Abiraterone Acetate (SAA).

We also refer to the meeting between representatives of your firm and the FDA on September 22, 2015. The purpose of the meeting was to discuss the format and content of a planned 505(b)(2) application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, September 22, 2015, 11:00 am – 12 Noon, EST
Meeting Location: White Oak Bldg. #22, Conf. Room 1421

Application Number: 115577
Product Name: SoluMatrix Abiraterone Acetate (SAA)
Indication: mCRPC
Sponsor/Applicant Name: Churchill Pharmaceuticals

Meeting Chair: V. Ellen Maher, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES

Geoffrey S. Kim, MD, Director, DOP 1
Amna Ibrahim, MD, Deputy Director, DOP 1
V. Ellen Maher, MD, Clinical Team Leader, DOP 1
James Xu, MD, Clinical Reviewer, DOP 1
Elimika Pfuma-Fletcher, Ph.D., Clinical Pharmacology Reviewer, DCPV
Jeanne Fourie-Zirkelbach, Ph.D., Clinical Pharmacology Reviewer, DCPV
Kimberly Ringgold, Ph.D., Non-Clinical Reviewer, DHOT
Wei Chen, Ph.D., Non-Clinical Reviewer, DHOT
Xiao-Hong Chen, Ph.D., Quality Assessment Lead, OPQ, ONDP
Olen Stephens, Ph.D., Acting Chemistry Branch Chief, OPQ, ONDP
Huiquan Wu, Ph.D., Chemical Engineer, OPQ, OPF
Bogdan Kurtyka, Ph.D., Quality Assessment Lead, OPQ, OPF
Jennifer Maguire, Ph.D., Acting Branch Chief, OPQ, OPF
Kim J. Robertson, Regulatory Health Project Manager, DOP 1

CHURCHILL PHARMACEUTICALS ATTENDEES

Satya Bhamidipati, Ph.D., Vice President, Process Development & Engineering, Churchill Pharmaceuticals LLC
Bill Bosch, Ph.D., Chief Scientific Officer, Churchill Pharmaceuticals LLC
Matt Callahan, CEO, Churchill Pharmaceuticals LLC
Jillian Chapas-Reed, M.S., Director, Clinical Operations, Churchill Pharmaceuticals LLC
(b) (4), R.Ph., Ph.D., Vice President, (b) (4)
Martha Manning, Esq., General Counsel, Churchill Pharmaceuticals LLC

CHURCHILL PHARMACEUTICALS ATTENDEES (cont.)
Scott Megaffin, President, Churchill Pharmaceuticals, LLC
Paul Nemeth, Ph.D., Vice President, Clinical Development & Regulatory Affairs, Churchill Pharmaceuticals LLC
Donald Sims, Ph.D., Director, Quality Assurance, Churchill Pharmaceuticals LLC
(b) (4)
(b) (4) Consultant Biostatistician, (b) (4).

1.0 BACKGROUND

Abiraterone acetate was approved in 2011 in combination with prednisone for the treatment of patients with metastatic castration resistant prostate cancer after docetaxel. Abiraterone has a large food effect and requires a 1,000 mg per day oral dose. Churchill Pharmaceuticals (Churchill) has developed a technology (b) (4) in an effort to increase absorption and bioavailability of the product, called Solumatrix Abiraterone Acetate (SAA).

After a pre-IND meeting on September 26, 2012, discussing the manufacturing, pharmacokinetic, and clinical study design issues, Churchill submitted IND 115577 for SAA on January 23, 2014. Churchill reported that 4 pharmacokinetic trials have been conducted in healthy, male volunteers, CHL-AA-101 (initial dose-finding study), CHL-AA-102 (BE study comparing single dose of 500 mg SAA and 1000 mg Zytiga in fasted conditions), CHL-AA-103 (the effect of a high-fat meal on the pharmacokinetics of 500 mg SAA), and CHL-AA-104 (comparison of a single dose of 500 mg SAA on background of methylprednisolone 4 mg bid at steady state to a single dose of 1000 mg Zytiga on a background of prednisone 5 mg bid at steady state). Churchill is seeking a 505(b)(2) pathway for approval of SAA, relying on existing supporting data for the abiraterone acetate approval except those data derived from the aforementioned 4 studies unique to SAA.

The preliminary review of the food effect trial (CHL-AA-103) shows that following a high-fat meal, the AUC of abiraterone (SAA formulation) increased 4.5 fold vs. an overnight fast. This food effect is much smaller than that observed with Zytiga, where a high-fat meal increased the AUC of abiraterone (Zytiga formulation) on average 10-fold vs. an overnight fast. Data from a new food effect study was added to the Zytiga PI in May 2015. These new data show that the abiraterone AUC was approximately 7-fold and 1.6 fold higher, respectively, when a single dose of Zytiga was administered 2 hours after or 1 hour before a medium fat meal, compared to an overnight fast. Therefore, the modified fasting condition recommended in the approved Zytiga label does not eliminate the food effect. The rate and extent of exposure to abiraterone in mCRPC patients treated with SAA may be less under the modified fasting condition vs. Zytiga. Since there are no adequate data to support an exposure-response relationship for efficacy for Zytiga, FDA is concerned that the lower exposure with SAA would result in a decreased overall survival advantage for SAA vs. Zytiga. In IRs dated July 2, 2015 and August 10, 2015, the Sponsor was notified that in light of the new data with Zytiga, and preliminary food effect data with SAA, PK equivalence would need to be shown under both fed and fasted conditions. If PK equivalence under both fed and fasted conditions is not shown, Churchill may need to assess the

safety and efficacy of the proposed formulation under the proposed dosing condition in a clinical trial compared to Zytiga. Churchill is requesting this meeting to further discuss with FDA the adequacy of their intended application.

FDA sent Preliminary Comments to Churchill Pharmaceuticals on September 18, 2015.

2. DISCUSSION

1. List of Final Questions Grouped by Discipline

REGULATORY AFFAIRS/OPERATIONS

BACKGROUND for Q9.1

Churchill Pharmaceuticals intends to submit a 505(b)(2) NDA in eCTD format via FDA's electronic submission gateway (ESG); in the submission draft product labeling will be submitted as SPL. Churchill has been informed by (b) (4), that (b) (4) will be updating the DMF (DMF (b) (4)) for the (b) (4) that Churchill has referenced in IND 115577 so that it can be referenced in the NDA for SAA. Churchill has chosen (b) (4), as a vendor to provide operational assistance in preparation of the submission and to submit the NDA through the ESG on Churchill's behalf.

In the 505(b)(2) NDA for SAA, Churchill Pharmaceuticals intends to rely on FDA's findings of safety and effectiveness for Zytiga insofar as they relate to nonclinical pharmacology and toxicology, clinical safety and efficacy, and clinical pharmacology except for what is unique to SAA as described in the results of studies CHL-AA-101, CHL-AA-102, CHL-AA-103 and CHL-AA-104 conducted by Churchill. Churchill does not have a right of reference to the source information except for the four clinical pharmacology studies conducted by Churchill. Therefore, for the NDA, Churchill intends to provide a statement in CTD summaries in module 2 that Churchill is relying on FDA's findings of safety and effectiveness for Zytiga.

In the case of Clinical Pharmacology, Churchill Pharmaceuticals also intends to include a Summary of Clinical Pharmacology for the studies it has conducted in the eCTD module 2 and the four clinical study reports for these four studies will be included in module 5. For the pivotal studies (i.e., CHL-AA-102 and CHL-AA-104), the datasets of PK parameters and relevant variables will be prepared in SAS transportable format with data description tables and included for each study under the sub-directory of study datasets in module 5.

The combined safety information from the 114 healthy male volunteers who have participated in the four Churchill Pharmaceuticals–sponsored trials will be included in module 5 as a report. Given the small number of subjects that are all male, all young and of normal BMI etc., no demographic breakdown of safety in subgroups of subjects is planned. For the study data tabulations under the study datasets in module 5, Churchill Pharmaceuticals intends to refer to

the Section 16 study data listings of each clinical study report that is included under the sub-directory of clinical study report in module 5.

9.1 Is this approach to the submission acceptable to the Division? Does the Division have any special requests relative to the design, format, etc. of the proposed NDA?

FDA RESPONSE: New data included in the current Zytiga package insert (IR: 8/10/15) show that the modified fasting condition was not adequate to eliminate the food-effect (FE) with Zytiga. Trial CHL-AA-102 shows PK equivalence between 500 mg SAA and 1000 mg Zytiga, however your FE trial shows a significantly lower FE for 500 mg SAA vs. 1000 mg Zytiga. Therefore, the SAA drug product does not perform in the same manner as the listed drug.

Your meeting package states that the rate and extent of exposure to abiraterone in mCRPC patients treated with SAA may be less under the modified fasting condition vs. Zytiga. Since there are no adequate data to support an exposure-response relationship for efficacy for Zytiga, we are concerned that the lower exposure with SAA would result in a decreased overall survival advantage for SAA vs. Zytiga.

Therefore, SAA under the proposed dosing conditions would need to be compared to Zytiga in a clinical trial, and results from such a trial should be included in your proposed NDA for SAA.

In your future NDA submission, we also request that you submit the datasets for the PK parameters for trials CHL-AA-103 and CHL-AA-101.

Meeting Discussion: The Sponsor will propose a clinical trial, comparing the effects of SAA and Zytiga on testosterone levels and other relevant biomarkers under the proposed dosing conditions, in a Type A meeting request.

BACKGROUND for Q9.2

As previously reviewed with the Division at the End of Phase 1 meeting held on July 18, 2014 and in follow up correspondence submitted July 24, 2014 and as updated, Churchill Plans to submit its 505(b)(2) NDA for SoluMatrix abiraterone acetate for use in combination with methylprednisolone for the treatment of metastatic castration resistant prostate cancer (b) (4)

(b) (4)

(b) (4)

[redacted]

9.2 Does the Division agree with the approach (b) (4) outlined above for the subject 505(b)(2) NDA application?

FDA RESPONSE: No. FDA does not comment on a Sponsor's planned patent certifications. (b) (4)

[redacted]

Meeting Discussion: No further discussions were necessary.

CLINICAL

BACKGROUND for Q9.3

On July 18, 2014, Churchill Pharmaceuticals had an End of Phase 1 meeting with the FDA. At that meeting the clinical pharmacology studies that Churchill Pharmaceuticals would need to do for the development of SAA were agreed. Those studies in healthy male subjects would:

1) establish that the 90% confidence intervals around the ratios of Cmax and AUC are within the limits (90% CI within 80 to 125%) that show bioequivalence (BE) of single doses of 500 mg of SAA and 1000 mg of Zytiga in fasted conditions.

2) show dose proportionality over the range of potential doses for SAA, i.e. from 125 mg to 500 mg.

3) establish equivalent single-dose exposure of SAA 500 mg + methylprednisolone 4 mg bid and single-dose Zytiga 1000 mg + prednisone 5 mg bid where methylprednisolone and prednisone have been dosed to steady state.

It was agreed that no studies in patients with metastatic castration-resistant prostate cancer (mCRPC) would be needed for the clinical development of SAA.

These requirements have been fulfilled by the following:

1) The results of study CHL-AA-102 demonstrate that a single dose 500 mg of SAA is bioequivalent to a single dose 1000 mg of Zytiga.

Table 1. Relative Bioavailability of SAA 500 mg vs Zytiga 1000 mg

PK parameters (No. of Subjects: 34)	Estimates	SAA 500 mg vs. Zytiga 1,000 mg
$AUC_{0\text{-}inf}$ (ng·hr/mL)	Geometric mean Ratio (%)	91.0
	90% CI	83.3 – 99.4 *
$AUC_{0\text{-}t}$ (ng·hr/mL)	Geometric mean Ratio (%)	93.4
	90% CI	85.3 – 102.4 *
C_{max}(ng/mL)	Geometric mean Ratio (%)	99.8
	90% CI	86.3 – 115.5 *

* Denotes 90% CI fell within the recommended 80.00-125.00% limits of bioequivalence.

2) The results of study CHL-AA-102 demonstrate that for SAA there is dose proportionality over the dose range of 125 mg to 625 mg.

Table 2. Bioequivalence Results of SAA 125 mg and 625 mg (Dose-Normalized to 500 mg)

PK parameters (No. of Subjects: 34)	Estimates	SAA 125 mg vs. 500 mg	SAA 625 mg vs. 500 mg
$AUC_{0\text{-}inf}$ (ng·hr/mL)	Geometric mean Ratio (%)	102.4	93.7
	90% CI	92.6 – 113.3 *	84.8 – 103.5 *

PK parameters (No. of Subjects: 34)	Estimates	SAA 125 mg vs. 500 mg	SAA 625 mg vs. 500 mg
AUC $_{0\text{-}t}$ (ng·hr/mL)	Geometric mean Ratio (%)	98.3	94.2
	90% CI	88.2 – 109.6 *	84.6 – 104.8 *
C_{max} (ng/mL)	Geometric mean Ratio (%)	132.3	97.3
	90% CI	111.9 – 156.4	82.6 – 114.8 *

* Denotes 90% CI fell within the recommended 80.00-125.00% limits of bioequivalence.

3) The results of study CHL-AA-104 demonstrate that for a single dose of SAA 500 mg on a steady state background of methylprednisolone 4 mg bid, the rate and extent of absorption of abiraterone are similar in magnitude to a single dose of 1000 mg Zytiga on a steady state background of prednisone 5 mg bid. There are no statistically significant differences ($p>0.05$) in the pharmacokinetic parameters Cmax, AUC(0-t), and AUC(0-inf) between the two test articles. Based on the bioequivalence approach of 80% to 125% limits of 90% confidence intervals on log scale, a single dose of SAA 500 mg on a background of methylprednisolone bid is bioequivalent to a single dose of Zytiga 1000 mg on a steady state background of prednisone 5 mg bid for AUC parameters. Further, the geometric mean ratio for Cmax is 1.168, but the upper level of the 90% confidence interval is 1.334 (see Table 3).

This lack of bioequivalence for Cmax may be due to a lower Cmax for Zytiga in study CHL-AA-104 in comparison to what was observed in study CHL-AA-101 and CHL-AA-102 (see Table 4).

Table 3. Relative Bioavailability of SAA 500 mg + methylprednisolone 4 mg bid vs Zytiga 1000 mg + prednisone 5 mg bid

PK parameters (No. of Subjects: 36)	Estimates	SAA 500 mg vs. Zytiga 1,000 mg
AUC $_{0\text{-}inf}$ (ng·hr/mL)	Geometric mean Ratio (%)	95.9
	90% CI	86.0 – 106.9 *
AUC $_{0\text{-}t}$ (ng·hr/mL)	Geometric mean Ratio (%)	99.2
	90% CI	88.7 – 110.9 *
C_{max}(ng/mL)	Geometric mean Ratio (%)	116.8
	90% CI	102.2 – 133.4

* Denotes 90% CI fell within the recommended 80.00-125.00% limits of bioequivalence.

Table 4. Maximum Mean Plasma Concentrations in Studies CHL-AA-101, CHL-AA-102, CH-AA-103 and CHL-AA-104

Study No.	Mean C_{max} (ng/mL)	
	SAA 500 mg	Zytiga 1000 mg
101 (Zytiga 1000 mg, fasted; N=19)	---	79.46
102 (SAA 500 mg vs Zytiga 1000 mg, fasted; N=34)	84.16	83.40
103 (SAA 500 mg, fasted; N=22)	75.84	---
104 (SAA 500 mg + methylprednisolone 4 mg bid vs Zytiga 1000 mg + prednisone 5 mg bid; N=36)	86.13	76.63

Finally, the results of CHL-AA-103 demonstrate a food effect on plasma abiraterone when a single dose of 500 mg of SAA is taken 30 minutes after a high-fat meal, i.e. relative to fasted conditions, Cmax and AUC are increased on average by 6.5X and 4.5X respectively. In comparison, the prescribing information for Zytiga describes a greater food effect on plasma abiraterone when a single dose of 1000 mg of Zytiga is taken after a high-fat meal, where relative to fasted conditions, Cmax and AUC are increased on average by 17X and 10X respectively.

9.3 Churchill Pharmaceuticals believes that sufficient clinical studies have been conducted and results generated for the FDA to accept a 505(b)(2) NDA for review. Does the Division agree? Does the Division agree that Churchill has established bioequivalence of SAA 500 mg to Zytiga 1000 mg in the fasted state, and has established dose proportionality over the range of potential doses for SAA (125 mg to 500 mg), and has demonstrated equivalent exposure of SAA 500 mg + methylprednisolone 4 mg bid and Zytiga 1000 mg + prednisone 5 mg bid (where methylprednisolone and prednisone have been dosed to steady-state)?

FDA RESPONSE: See response to Question 9.1 for additional studies needed in the NDA. Your data to show PK equivalence of SAA 500 mg to Zytiga 1000 mg in the fasted state, dose proportionality over the range of potential does for SAA (125 to 500 mg), and equivalent exposure of SAA 500 mg + methylprednisolone 4 mg bid and Zytiga 1000 mg + prednisone 5 mg bid appear acceptable. A final determination will be made during the NDA review.

Meeting Discussion: No further discussions were necessary.

BACKGROUND for Q9.4

On July 2, 2015, FDA sent Churchill the following e-mail:

> *We refer you to updated information regarding food effect included in Section 12.3 of the Zytiga label. Recent data indicates the modified fasting conditions used in the approved labeling for Zytiga do not eliminate the food effect. Please note that in light of the new data, if you develop a product that is not bioequivalent to Zytiga under both fasted and fed (high-fat) conditions, you may need to assess the safety and efficacy of your selected formulation under your proposed dosing conditions in a clinical trial compared to Zytiga. We recommend you discuss with the Agency your development plan in consideration of the current data.*

Subsequently on July 31, 2015, FDA sent Churchill an additional related e-mail message:

> *With regards to the upcoming scheduled September 22, 2015 meeting between the FDA and Churchill Pharma:*
>
> *We refer you to the information request dated 07/02 referring you to new data showing that the modified fasting conditions used in the approved labeling for Zytiga do not eliminate the food effect. We noted that in light of the new data, if you develop a product that is not bioequivalent to Zytiga under both fasted and fed (high-fat) conditions, you may need to assess the safety and efficacy of your selected formulation under your proposed dosing conditions in a clinical trial compared to Zytiga.*
> *Discuss your development plan at the upcoming meeting (09/22/2015), considering both the lower food effect observed at the proposed 500 mg dose of Solumatrix compared to that observed at the 1000 mg dose of Zytiga (cross-study comparison), and the new data (information request dated 07/02). Your proposal should address concerns about a potential for decreased efficacy at the proposed 500 mg dose of Solumatrix compared to the approved dose of Zytiga if used in the same dosing conditions as Zytiga. In addition, your proposal should consider that a potential for differential food effects can be observed at different doses of abiraterone acetate. Refer to an abstract presented at AACR-NCI-EORTC International Conference:* Molecular Targets and Cancer Therapeutics-- Oct 22-26, 2007; San Francisco, CA titled "Effect of concomitant food intake on pharmacokinetics of abiraterone acetate, a 17 α hydroxylase C17,20-lyase inhibitor in castration-resistant prostate cancer (CRPC)."

Churchill welcomes the opportunity to discuss the development plan for SAA with the Agency.

Churchill does not believe that the lower food effect observed in healthy volunteers at the proposed dose of 500 mg of SAA compared to the labeled food effect in healthy volunteers for 1000 mg of Zytiga would result in decreased efficacy in patients if SAA is administered on an empty stomach, i.e. (b) (4)

(b) (4) Churchill acknowledges that the rate and extent of exposure to abiraterone in mCRPC patients treated with 500 mg of SAA may be somewhat less, under the modified fasting conditions that define administration on an empty stomach, in comparison to 1000 mg of Zytiga. However, Churchill believes that the exposure to abiraterone will be within the limits of variability for patients treated with 1000 mg of Zytiga and adequate to provide comparable efficacy to Zytiga for the following reasons:

A. Zytiga is a Highly Variable Drug

The updated information regarding food effect included in Section 12.3 of the Zytiga label (May, 2015) is consistent with what was already known at the time that Zytiga was approved, i.e. that the mean exposures appear higher in patients than in healthy volunteers (FDA Clinical Pharmacology and Biopharmaceutics Review(s) for NDA 202-379, 2011) likely due to the difference in fasting conditions. Page 22 of that review describes a possible basis for the findings:

> *Although the mean exposures appear higher in patients, the results are confounded by the use of fasting (over night fast and no food for 4 hours post dose) in healthy volunteer studies versus the use of modified fasting (no food for at least 2 hours before or 1 hour after dose) in the patient studies.*

The paragraph of the FDA review with the above text concludes:

> *However, the difference in exposures between patients and healthy volunteers is within the limits of inter-individual variability observed for abiraterone and is likely not clinically relevant.*

Based on BE in fasted healthy volunteers and comparable (CHL-AA-102 and CHL-AA-103) or reduced (CHL-AA-104) pharmacokinetic variability for 500 mg of SAA relative to 1000 mg of Zytiga, Churchill believes that the rate and extent of exposure to abiraterone in mCRPC patients treated with 500 mg of SAA will be well within the limits of variability for mCRPC patients treated with 1000 mg of Zytiga.

B. Abiraterone Acetate is to be Taken on an Empty Stomach

We note that the basis for the update to the prescribing information for Zytiga on May 2015 is two small studies that were conducted by the sponsor of the reference product in patients and healthy volunteers. In healthy male volunteers, a medium-fat meal given 1 hour after administration of Zytiga increased AUC by 1.6-fold, and the medium-fat meal given 2 hours before administration of Zytiga increased AUC by 7-fold. No changes to the Zytiga Dosage and Administration Section of the label were made as a result of the inclusion of these data in Section 12.3. Indeed, the Pharmacokinetics Section of the label continues to emphasize the importance of taking Zytiga in the fasted state with the following statements:

> *Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures.*

> *Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken.*

Furthermore, a recent published report (Chi et al., J Clin Pharmacol, 2015) of a study in mCRPC patients (one of the studies that was the basis for the update to the prescribing information for Zytiga on May 2015), which includes authors from the sponsor of the reference product, Zytiga, showed a lesser effect of a high-fat meal, i.e. ~2-fold higher AUC, and similar AUC with low-fat meal vs modified fasting state, and concludes:

> *... that short-term inadvertent administration of abiraterone-prednisone with food would appear to have minimal, if any, impact on safety.*

According to the Dosage and Administration Section and Section 12.3 of the label, Zytiga is not intended to be taken 30 minutes after a high-fat meal in the treatment of mCRPC patients, but rather is to be taken only on an empty stomach (i.e. the product should be administered at least 1 hour before or 2 hours after a meal). The FDA draft guidance for Industry: "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" December 2013. The draft guidance on Fed Bioequivalence Studies is:

> *When a fasting in vivo BE study is recommended for an orally administered, immediate release product, we recommend that applicants conduct a fed study, except when the dosage and administration section of the RLD labeling states that the product should be taken only on an empty stomach (e.g., the labeling states that the product should be administered 1 hour before or 2 hours after a meal).*

The specific FDA Draft Guidance on Abiraterone Acetate (Recommended Dec 2012; Revised Feb 2014) is consistent with this general BE guidance for ANDAs cited above, i.e. one study in fasted conditions in healthy male volunteers is required.

Churchill believes its current package of completed studies is adequate to support its 505(b)(2) NDA. (b) (4)

Additionally, Churchill agreements with FDA at the pre-IND meeting and the end-of-phase 1 meeting for SAA for demonstration of BE under fasted conditions alone should continue to be applicable because the new information in the Zytiga label is consistent with what was known at the time that Zytiga was approved and has not led to a change in the Dosage and Administration for Zytiga. Furthermore, FDA's conclusions in the Clinical Pharmacology and Biopharmaceutic Review(s) for Zytiga should still apply.

Churchill has demonstrated that a single dose 500 mg of SAA is BE to a single dose 1000 mg of Zytiga in healthy male volunteers in fasted conditions (CHL-AA-102). Churchill has also evaluated the effect of food on the pharmacokinetics of SAA in study CHL-AA-103 which demonstrated that when 500 mg of SAA is administered 30 minutes after a high-fat meal in healthy male volunteers, Cmax increases approximately 6.5-fold and AUC increases approximately 4.5-fold. Thus, the magnitude of the food effect for SAA may be less than half of

the labelled food effect for Zytiga which has 17-fold and 10-fold increases for Cmax and AUC when Zytiga is dosed with the same schedule and subject type. Given that the food effect with regard to Cmax and AUC for SAA in the CHL-AA-103 study was less than half that of Zytiga, it is unlikely that single dose 500 mg of SAA would be BE to single dose 1000 mg of Zytiga after a high-fat meal. Although a lesser food effect is likely within the limits of inter-individual variability observed for abiraterone and is likely not clinically relevant, if there is relevance, it would be in favor of safety by limiting excess exposure to abiraterone from 500 mg of SAA.

C. The Mechanism of Action of Abiraterone Acetate is Inhibition of the CYP 17 Enzyme and there is Strong Evidence that Inhibition of the CYP 17 Enzyme Occurs at Plasma Concentrations Corresponding to Fasting Abiraterone Acetate Doses Below 1000 mg

In the absence of an established PK/PD relationship for safety or efficacy measures that would suggest that higher plasma concentrations are needed for efficacy, the closest link to efficacy is to provide adequate exposure to ensure inhibition of the CYP 17 enzyme. Since the mechanism of action of abiraterone is inhibition of steroid synthesis via inhibition of the CYP17 enzyme, 500 mg of SAA should provide adequate rate and extent of exposure to inhibit this enzyme and have comparable efficacy to Zytiga.

Specifically, the abstract referred to us on July 31, 2015 (Ryan et al., 2007) describes a study in which 27 mCRPC patients were treated with abiraterone acetate 250 mg, 500 mg, or 750 mg in fed or fasted conditions and at 1,000 mg in fasted conditions only. No significant food effects were observed at the 250 mg dose level, while food increased Cmax and AUC by 2- to 5-fold at the 500 mg and 750 mg dose levels respectively. PSA levels before and after treatment were measured, with responders defined as having a confirmed PSA decline of >50%. Responses by food state and dose are: 250 mg, 2 of 3 fasted, 0 of 3 fed; 500 mg, 4 of 6 fasted, 1 of 3 fed; 750 mg, 1 of 3 fasted, 3 of 3 fed; 1000 mg, 3 of 6 fasted. Exposure to abiraterone after abiraterone acetate was dosed at 500 mg or 750 mg under fasted conditions was equally adequate to inhibit this enzyme as the same doses of abiraterone acetate under fed conditions, i.e.

> *No difference between fed and fasted groups in adrenal metabolites levels or safety is observed.* (Ryan et al., 2007).

Based on the small number of patients in this study, the effect of food on the efficacy of abiraterone acetate is unclear. However, there is good evidence as measured by PSA response that inhibition of the CYP17 enzyme occurred even at doses as low as 250 mg under fasted conditions, and that the lower exposures associated with fasted conditions at the 500 mg and 750 mg dose levels relative to fed conditions did not affect adrenal metabolite levels.

Furthermore, the exposure to 750 mg of Zytiga provides near maximal inhibition of this enzyme:

> *A near maximal increase was observed in the mean deoxycorticosterone and corticosterone (steroids upstream of CYP17 that may serve as biomarkers of the completeness of CYP17 inhibition) levels at the 750 mg dose whereas higher doses of 1000 mg and 2000 mg did not further raise the levels. Testosterone and*

androstenedione concentrations were below the lower limit of detection at the three doses. (FDA Clinical Pharmacology and Biopharmaceutics Review(s) for NDA 202-379, 2011)

D. 750 mg of Zytiga Appears to be an Effective Dose in Patients Requiring Dose Reduction

Finally, a further point of consistency is that 750 mg of Zytiga appears to continue to have efficacy in the setting of dose reduction following hepatotoxicity. A total of 28 patients treated with abiraterone acetate had dose reductions during the key study supporting the NDA. Twenty-one had a dose reduction to 750 mg and 11 patients had a maximum dose reduction to 500 mg. To explore whether dose reductions affected the treatment effect or antitumor activity of abiraterone acetate, differences in PSA response rates between treatment periods at the original dose level and the reduce dose levels were analyzed (FDA Clinical Review of NDA 202379, p. 60-61). The review concludes:

The results suggest that the dose reductions were associated with similar PSA responses compared to the PSA responses observed prior to the reductions in these patients. In addition, PSA declines of 50% also occurred or continued at the dose level of either 750 mg or 500 mg, suggesting that the antitumor activity remained with a dose reduction in patients responding to abiraterone acetate treatment. This finding also supports the proposed dose reduction recommendations in the product label.

Thus, 500 mg of SAA will provide adequate exposure to inhibit the CYP 17 enzyme. With the equal ability to inhibit this enzyme, 500 mg of SAA should have comparable efficacy to 1000 mg of Zytiga.

9.4 Churchill believes that the demonstration of BE of single dose 500 mg of SAA to single dose 1000 mg of Zytiga under fasting conditions, the demonstration of dose proportionality over the range of 125 mg to 625 mg, and the demonstration of the lesser effect of a high-fat meal on the rate and extent of exposure to abiraterone from 500 mg of SAA compared to Zytiga 1000 mg, provides adequate information to support (b) (4) [redacted]. Does the Agency agree?

FDA RESPONSE: No. Please see response to Question 9.1.

Meeting Discussion: No further discussions were necessary.

BACKGROUND for Q9.5

For module 3, Churchill will rely on reference to a (b) (4) DMF for the drug substance and an (b) (4) DMF for the (b) (4). For the relevant portions of module 3, letters of authorization from (b) (4) and (b) (4) will be provided. Certificates of analysis for the lots of drug substance used in the manufacture of the three NDA qualification lots of drug product will

also be provided. The rest of module 3 will include the description and results of the testing of the [redacted] 125 mg SAA tablets at [redacted], the container closure and available accelerated stability results at high temperature and humidity as well as one-year stability at standard room temperature and humidity reports on the NDA qualification lots. Churchill intends to amend the NDA for SAA with 18 month stability reports on the qualification lots of drug product at least three months in advance of the user fee date set for the completion of NDA review period.

9.5 Is this approach acceptable to the FDA?

FDA RESPONSE: Question 9.5 is vaguely written, so it is only possible to respond in generalities regarding your proposed filing strategy. The proposal to rely on DMFs for the drug substance and [redacted] may be acceptable pending review of the data in the DMFs. The control strategy within the DMFs and at the [redacted] manufacturing site will be critical to the overall control strategy, in particular, release testing from the drug substance and [redacted] manufacturers, hold times, transportation studies, and acceptance criteria and testing. The proposal to provide CoA's for the lots of drug substance used in the manufacture of three NDA qualification lots of drug product is acceptable. Regarding the submission of a complete NDA, in general, 12 months of long term stability data from three batches of primary stability data is expected in the original NDA submission. Refer to ICH Q1A. The updated stability data should be submitted within 30 days from the original NDA submission. Stability data submitted after the 30-day period may or may not be reviewed based on available resources.

We consider the [redacted] operation. In the NDA submission, provide data for both the drug substance and the excipients that undergo [redacted] Comment on the clinical impact (safety and/or efficacy) of this operation, its reproducibility from batch-to-batch, and the correlation between the critical quality attributes of the [redacted] to the quality target product profile. Identify the critical process variables, critical material attributes of the excipients and drug substance, and critical quality attributes of the [redacted], and provide experimental data (preferably multivariate data) to demonstrate that the proposed control strategy for the [redacted] ensures a robust manufacturing process capable of delivering consistent quality final drug product.

We understand that the manufacturing process can include other [redacted] steps, not described in the meeting package. The acceptability of the manufacturing process and its control strategy will be assessed during NDA review based on the overall data submitted.

Meeting Discussion: The Agency emphasized the need for a strong overall control strategy between Churchill and the DMF holder of the [redacted], regarding the [redacted] release, testing, and acceptance of material at the final drug product manufacture.

BACKGROUND for Q9.6

Sodium lauryl sulfate is used as [redacted]

The anticipated daily dose of SAA is 4 x 125 mg which corresponds to a daily intake of [redacted] mg of sodium lauryl sulfate. For a 70 kg individual, this equates to an oral exposure level of [redacted] mg/kg. A human health risk assessment for sodium lauryl sulfate can be found in the August 5, 2009 United States Environmental Protection Agency Memorandum entitled "Sodium Lauryl Sulfate. Human Health Risk Assessment to Support Proposed Exemption from the Requirement of a Tolerance When Used as an Inert Ingredient in Pesticide Formulations." The Memorandum reports a no-observed adverse effect level of 100 mg/kg/day for subchronic oral administration based on a 28-day oral gavage study in rats. The Memorandum also reports that no treatment related effects were observed in two 2-year rat feeding studies at doses up to approximately 100 mg/kg/day. Therefore, the expected daily exposure to sodium lauryl sulfate for patients taking SAA Tablets 125 mg is substantially lower than the no-observed adverse effect levels established for sodium lauryl sulfate in subchronic toxicology studies.

Publications referenced in this and an earlier (July 31, 2006) US EPA Memorandum include peer-reviewed reports of toxicity studies on alkyl sulfates [Walker et al, 1967. Toxicity of Sodium Lauryl Sulphate, Sodium Lauryl Ethoxysulphate and Corresponding Surfactants Derived from Synthetic Alcohols. Food and Cosmetic Toxicology 5: 763-769. Palmer et al, 1975. Assessment of the teratogenic potential of surfactants. Part I-LAS, AS and CLD. Toxicology 3(1): 91-106]. Reference is also made to the human health risk assessment performed as part of the Human & Environmental Risk Assessment (HERA) on ingredients of household cleaning products.

Finally, SAA Tablets (125 mg) have been administered to a total of 98 healthy male subjects in clinical trials CHL-AA-102, CHL-AA-103, and CHL-AA-104. The subjects in CHL-AA-102 (n=36) received doses of 1 x 125 mg, 4 x 125 mg, and 5 x 125 mg while the subjects in CHL-AA-103 (n=25) and CHL-AA-104 (n=37) each received 4 x 125 mg of SAA. In all of these studies there were no differences in the adverse event profiles relative to the comparator product Zytiga.

9.6 The proposed commercial formulation for SAA Tablets 125 mg contains (b) (4) mg of sodium lauryl sulfate per tablet. Does the Agency agree that no further justification or qualification of this level of sodium lauryl sulfate is required? Is this approach acceptable to the Division?

FDA RESPONSE: Your approach appears acceptable to support submission of an NDA. A final decision on whether the safety of your drug product has been adequately assessed will be made after review of an NDA, which should include your complete justification for the levels of sodium lauryl sulfate in your abiraterone acetate drug product.

Meeting Discussion: No further discussions were necessary.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

N/A

5.0 ACTION ITEMS

N/A

6.0 ATTACHMENTS AND HANDOUTS

N/A

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

/s/

VIRGINIA E MAHER
11/16/2015