CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213953Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118675

MEETING MINUTES

Marius Pharmaceuticals, LLC
Attention: Craig Metz, Ph.D.
SVP Regulatory Affairs
8601 Six Forks Road, Suite 630
Raleigh, NC 27615-2965

Dear Dr. Metz:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOV2012-F1 (oral testosterone undecanoate).

We also refer to the teleconference between representatives of your firm and the FDA on July 22, 2020. The purpose of the meeting was to discuss and obtain FDA comments on specific clinical aspects of your upcoming New Drug Application (NDA) submission.

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

If you have any questions, call Jeannie Roule, Regulatory Health Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Suresh Kaul, M.D., M.P.H.
Medical Team Leader, Urology
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: **B**
Meeting Category: **Pre-NDA**

Meeting Date and Time: **July 22, 2020, 1:00 to 2:00 PM**
Meeting Location: **Teleconference**

Application Number: **118675**
Product Name: **Testosterone undecanoate (SOV2012-F1)**

Indication: **Testosterone replacement therapy in adult men**
Sponsor Name: **Marius Pharmaceuticals**

Regulatory Pathway: **505(b)(2) of the Food, Drug, and Cosmetics Act**

Meeting Chair: **Suresh Kaul**
Meeting Recorder: **Jeannie Roule**

FDA ATTENDEES

Christine Nguyen, M.D.	Director (acting), Division of Urologic, Obstetrics and Reproductive Products (DUOG)
Suresh Kaul, M.D., MPH.	Medical Team Leader, DUOG
Jordan Dimitrakoff, M.D., Ph.D.	Medical Officer, DUOG
Martin Kaufman, D.P.M., M.B.A.	Sr. Clinical Analyst, DUOG
Kimberley Hatfield, Ph.D.	Pharmacology/Toxicology Team Lead, Division of PharmTox, Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT-RPURM)
Yanhui Lu, Ph.D.	Team Lead, Clinical Pharmacology, OCP, Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
Chongwoo Yu, Ph.D.	Clinical Pharmacology Reviewer, OCP, DCEP
Daphne Lin, Ph.D.	Team Leader, Division of Biometrics (DB) III, Office of Translational Sciences (OTS)
Jia Guo, Ph.D.	Statistical Reviewer, DB IV, OTS
Hong Cai, Ph.D	CMC Team Lead, Office of Pharmaceutical Quality (OPQ), Office of New Drug Policy (ONDP), Division of New Drug Products II (DNDPII)
Samantha Bell	Chief (acting), Project Management Staff, Division of Regulatory Operations for Urology, Obstetrics, and Gynecology

Jeannie Roule	Senior Regulatory Health Project Manager, Division of Regulatory Operations for Urology, Obstetrics, and Gynecology

SPONSOR ATTENDEES

Om Dhingra, Ph.D.	Chief Executive Officer
James Bernstein, Ph.D.	Chief Scientific Officer
Craig Metz, Ph.D.	Senior Vice President, Regulatory Affairs
Roger Rittmaster, M.D.	Chief Medical Officer, Marius Pharmaceuticals
(b) (4)	Consulting Biostatistician to Marius Pharmaceuticals
(b) (4)	Consultants to Marius Pharmaceuticals

BACKGROUND

Marius Pharmaceuticals has developed a novel oral formulation of testosterone undecanoate (TU), SOV2012-F1, as testosterone replacement therapy for primary and secondary hypogonadism. SOV2012-F1 is a soft gelatin capsule containing (b) (4)

A 12-month phase 3 clinical trial in adult hypogonadal men (MRS-TU-2019) began in July 2017, with the last subject randomized in March of 2018. A 6-month extension of the phase 3 study, MRS-TU-2019EXT, was initiated in September 2018, and will provide the primary efficacy and ambulatory blood pressure monitoring (ABPM) data for the NDA. These data, along with data from phase 1 and phase 2 studies will form the basis for an NDA for SOV2012-F1.

On October 23, 2019, Marius submitted a Clinical Study Report of MRS-TNR2019, a study to determine the normal range of systemic testosterone and dihydrotestosterone (DHT) concentrations from plasma collected in NaF/EDTA tubes and serum in plain tubes, respectively, from healthy, eugonadal male subjects aged 18-40 years. The bioanalytical study report for the NaF/EDTA plasma samples for MRS-TNR2019 was submitted on November 13, 2019.

On January 27, 2020, the Division responded to questions that were posed in a Written Responses Only (WRO) meeting request. The Sponsor's questions were regarding the following:

- Normal range for systemic testosterone concentrations using plasma samples obtained with NaF/EDTA tubes
- The approach for setting Cmax safety criteria appropriate to testosterone values measured in the NaF/EDTA plasma matrix, starting from the accepted serum-based Cmax safety criteria (1500, 1800, and 2500 ng/dL)
- Derivation of a factor to convert the titration thresholds from a NaF/EDTA-based plasma assay (used in the clinical trials) to those appropriate for a serum-based assay as would be proposed for use in clinical practice.

A separate pre-submission meeting was held on April 6, 2020, to discuss Chemistry, Manufacturing, and Controls for SOV2012-F1. Official meeting minutes were issued on April 18, 2020.

The objective of this meeting request is to obtain FDA comment on specific clinical aspects of the SOV2012-F1 NDA, including the following:

- Primary efficacy and safety data (Cavg and Cmax) from study MRS-TU-2019EXT
- Ambulatory blood pressure monitoring (ABPM) results from MRS-TU-2019EXT
- Exclusion of a clinical site for non-compliant sample handling
- Discussion of Marius' approach for supporting a post-dose window for obtaining a T measurement for titration purposes
- Adaptation of NaF/EDTA Plasma thresholds to Serum-based thresholds for clinical use
- Discussion of food effect and alcohol interaction results
- Scope of Post-Marketing Data in NDA
- Pediatric Study Plan
- Environmental Assessment

QUESTIONS AND DISCUSSION
Preliminary responses were provided to the Sponsor on July 20, 2020, in response to the questions posed in the Sponsor's meeting package provided to FDA on June 19, 2020.

In addition, on July 21, 2020, the Sponsor submitted (via email) responses to our preliminary comments. The Sponsor requested further clarification for Questions 1, 2, 5 and 6.

The Sponsor's questions are presented below in bolded font, followed by the Division's preliminary responses in normal text.

Discussion that occurred during the meeting is shown after the preliminary responses in *italicized* font, under the heading *Additional Discussion.* FDA's post-meeting comments are also shown in *italicized* font.

Question 1: Primary Efficacy
Does the Agency have any comments or questions regarding these data at the present time?

FDA Response:
In general, the submitted data appear reasonable. However, a final assessment of efficacy will be made at the time of NDA review.

The exclusion of site 104 will be a review issue. Include C_{max} analysis, both with and without Site 104 data, with your justification and supporting data. For subjects from Site

104, submit specific rationale of why each subject needs to be excluded from the efficacy and/or C_{max} analysis.

Additional Discussion:
Regarding Site 104, Marius reiterated that even when samples were handled in accordance with the instructions contained in the protocol, average serum T-concentrations exceeded average NaF/EDTA plasma T concentrations, due to the increased degradation of TU to T and analytical matrix effects. Marius further stated that the nature of NaF/EDTA plasma concentrations at Site 104 were not limited to extremely high concentrations only, but occurred even at serum values that were within the normal range.

Therefore, Marius believes that the plasma PK data from Site 104 should be excluded from the primary efficacy and safety analyses. To support this approach, Marius presented data in two 24-hour T-concentration PK figures (see attached). Figure 1 was from Site 104 with the plasma and serum T levels inverted. Figure 2 was from site 109 in which the plasma and serum T levels were aligned as usually seen in subjects whose plasma samples were processed according to the protocol. Marius clarified their approach for the outlier analysis based on using the total population of serum/plasma pairs, identifying outliers in that population, and subsequently filtering out PK profiles that contain one or more outlier data points.

Marius inquired if subject-by-subject justification for exclusion from the primary efficacy and safety analyses was required by the FDA.

Marius also pointed out that all 5 subjects with C_{max} T-levels greater than 2000 ng/dL (2.5 X Upper Limit of Normal for T in NaF/EDTA plasma) were from Site 104.

The FDA clarified that it was asking sponsors to provide narratives for subjects where C_{max} exceeded 1.5 X the upper limit of the normal T range (i.e. the proposed 1200 ng/dL in this case). The FDA further stated that individual narratives supporting exclusion of the Site 104 plasma PK data, and review of overall efficacy and safety profile of the drug product along with data validity will be a review issue.

Question 2: Cmax
Does the Agency have any comments or questions regarding this data at the present time?

FDA Response:
Refer to our response to Question 1.

Additional Discussion:
See additional discussion under Question 1.

Question 3: ABPM and Vital Signs Data
Does the FDA have any questions or advice to offer regarding these data at the present time?

FDA Response:
While we do not have any advice regarding the data presentation, we note that the conclusion in the meeting package of (b) (4)

When you submit your ambulatory blood pressure monitoring (ABPM) study report, we request that you include the following:

a. Electronic datasets as SAS.xpt transport files (in CDISC SDTM and ADaM format – if possible) and all the SAS codes used for the primary statistical analysis.
b. An analysis dataset that contains the columns defined in the metadata tables below.

Table 1: Analysis Variable Metadata for ADSL

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
STUDYID	Study Identifier	Char		
USUBJID	Unique Subject Identifier	Char		
ARM	Description of Planned Arm	Char		
ACTARM	Description of Actual Arm	Char		
TRTxxP	Planned Treatment for Period xx	Char		
TRTxxA	Actual Treatment for Period xx	Char		
AGE	Age	Num		
AGEU	Age Units	Char		
RACE	Race	Char	Race	
RACEC	Race as collected	Char	Race As Collected	
ETHNIC	Ethnicity	Char	Ethnicity Group	
ETHNICC	Ethnicity as collected	Char	Ethnicity As Collected	
BLBMI	Baseline BMI	Num		Baseline BMI in kg/m^2
BLWT	Baseline Weight	Num		Baseline weight in kg
BLHT	Baseline Standing Height	Num		Baseline standing height in cm

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
BLTCL	Baseline total cholesterol	Num		Baseline Total cholesterol in mg/dL
BLHDL	Baseline HDL cholesterol	Num		Baseline HDL cholesterol in mg/dL
BLSBP	Baseline Systolic BP	Num		Baseline systolic BP in mmHg
BLDBP	Baseline Diastolic BP	Num		Baseline diastolic BP in mmHg
PXHTNFL	Prior history of hypertension	Char	'Y'	Prior history of hypertension at baseline
DIABFL	Diabetes	Char	'Y'	Diabetes at baseline
SMOKFL	Smoking	Char	'Y'	Smoking status at baseline
BPTRTFL	Treated blood pressure	Char	'Y'	Treated blood pressure at baseline

Table 2: Analysis Variable Metadata for ADBP

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
STUDYID	Study Identifier	Char		
USUBJID	Unique Subject Identifier	Char		
TRTSEQP	Planned Sequence of Treatments	Char		
TRTP	Planned Treatment	Char		
TRTPN	Planned Treatment (N)	Num		The numeric code for TRTP. One-to-one mapping within ADBP to TRTP.
TRTSEQA	Actual Sequence of Treatments	Char		
TRTA	Actual Treatment	Char		
TRTAN	Actual Treatment (N)	Num		The numeric code for TRTA. One-to-one mapping within ADBP to TRTA.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
PARAM	Parameter	Char	VSTEST	For records with a corresponding record in VS test results (VS) dataset (e.g., for systolic blood pressure, "Systolic Blood Pressure ").
PARAMCD	Parameter Code	Char		One-to-one correspondence with PARAM. For records with a corresponding record in VS, PARAMCD should be VS.VSTESTCD.
PARAMN	Parameter (N)	Num		Numeric code for PARAM. One-to-one correspondence with PARAM.
APERIOD	Period	Num		Populate based on VS.VISITNUM.
APERIODC	Period (C)	Char		Character version of APERIOD. One-to-one correspondence with APERIOD.
AVISIT	Analysis Visit	Char		Populate based on VS.VISIT.
AVISITN	Analysis Visit (N)	Num		Numeric version of AVISIT. Since study visits are usually defined by certain time points, defining AVISITN so that it represents the time point associated with the visit can facilitate plotting and interpretation of the values. Alternatively, AVISITN may be a protocol visit number, a cycle number, an analysis visit number, or any other number logically related to AVISIT or useful for sorting that is needed for analysis (see ADaM IG).

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
DTYPE	Derivation Type	Char	DTYPE	Denotes if an observation is a derived value (e.g., average within time-window such as 24-h, 0-1 h post-dose or 5-6 pm). If a derivation other than average was used, then the derivation should be documented.
ATPTGR	Analysis Time Group	Char		Denotes the Analysis Time Group, used only for derived records (DTYPE <> “”). Reserved values: “Visit average”: Standard visit averages (24-h, Awake, Asleep) “Hourly average”: Hourly averages per visit
ATPTGRN	Analysis Time Group (N)	Num		Denotes the ordering of Analysis Time Groups.
ATPT	Analysis Time Point	Char		Denotes analysis time-point, only populated for derived records. Reserved values: “24-h”, “Sleep”, “Awake”
ATPTN	Analysis Time Point (N)	Num		ATPTN provides a numeric representation of ATPT. Only populated for derived values. Reserved values: “24-h” (1), “Asleep” (2), “Awake” (3)
ATPTREF	Analysis Reference Time Point	Char		Denotes the methodology for deriving start and stop for a specific ATPT. For example, if ATPT is “Asleep”, then this column describes how the start and stop for this window was derived, e.g. via clock time or diary. Similarly, if ATPT describes an hourly range

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
				(e.g., 00:00 to 01:00) then ATPTREF should describe if that is relative to a given dose or to midnight. Reserved values: “Clock”, “Diary”, “Actigraphy”
ASTDTCz	Analysis Time Point Start Time	Char		Actual time of the start of the corresponding ATPT. Permits selecting all corresponding DTYPE eq “” that were used to calculate the derived value. Pairs with AENDTCz as an OR, e.g., if a value is within ASTDTC1 and AENDTC1 or ASTDTC2 and AENDTC2 then it is within the window.
AENDTCz	Analysis Time Point End Time	Char		Actual time of the stop of the corresponding ATPT. Pairs with ASTDTCz.
ATPTEX	Number of Expected Values	Num		Number of expected values per protocol for derived value. For example, if the protocol included 2 measurements per hour, then this value would be 48 for all subjects for the 24-h average.
ATPTOB	Number of Observed Values	Num		Number of values observed within a time-window. Should correspond to the number of measurements within ASTDTCz and AENDTCz.
ADTM	Analysis Date and Time	Num		Populate from VS.VSDTC.
ADT	Analysis Date	Num		Numeric date value from VS.VSDTC.
ATM	Analysis Time	Num		Numeric time value from VS.VSDTC.
ADY	Analysis Relative Day	Num		Populate based on VS.VSDY.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
AVISDY	Analysis Visit Day	Num		
APERDAY	Analysis Nominal Period Day	Num		Populate with the numeric relative day within the Period based on AVISITN. For example, "Period 2 Day 1" is APERDAY=1.
AVAL	Analysis Value	Num		Populate with VS.VSSTRESN for non-derived records. For derived records, this value reflects the derived value for that derived group.
AVALU	Units of Analysis Value	Char	UNIT	Populate with VS.VSSTRESU. For derived values, AVALU might need to be changed depending on the derivation.
ABLFL	Baseline Record Flag	Char	Y	Character indicator to identify the baseline record for each subject, parameter, and baseline type (BASETYPE) combination.
BASE	Baseline Value	Num		The subject's baseline analysis value for a parameter and baseline definition (i.e. BASETYPE). BASE contains the value of AVAL copied from a record within the parameter on which ABLFL eq "Y" and same BASETYPE. Note that a baseline record may be derived (e.g., it may be an average) in which case DTYPE should be populated on the baseline record.
CHG	Change from Baseline	Num		If ABLFL ne "Y" and DTYPE eq "AVERAGE" then CHG=AVAL – BASE.
BASETYPE	Baseline Type	Char		Encodes the key that allows for identifying baseline rows that correspond to each

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
				DTYPE eq ”AVERAGE” and ABLFL ne “Y”.
VSSEQ	Sequence Number	Num		Populate with VS.VSSEQ. Missing for derived records.
CRITy	Analysis Criterion y	Char		A text string identifying a pre-specified criterion within a parameter, for example Systolic BP ≥ 160. Required if CRITyFL exists (see ADaM IG).
CRITyFL	Criterion y Evaluation Result Flag	Char	Y	Character flag variable indicating whether the criterion defined in CRITy was met by the data on record. See CRITy for more information regarding how to use CRITy and CRITyFL to indicate whether a criterion is met (see ADaM IG).
SPDEVID	Sponsor Device Identification	Char		Sponsor-defined identifier for the device.
QUALFL	Quality Check Flag	Char	Y	Character flag variable set to “Y” if the record is defined as good quality observation by protocol or null otherwise.
BPTYPE	Blood pressure technique type	Char		Describes the blood pressure modality used. Reserved key words: “ABPM”, “Cuff”
RECID	Record ID	Char		Used to capture all ADBP entries that are from the same recording. Only populated for DTYPE eq ‘’

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
VCRTyy	ABPM Validity Criterion y	Char		Describes the validity criteria used. Each validity criteria will have VCRTyy and VCRTyyFL to describe the yyth criterion (VCRTyy) and whether or not the ABPM record satisfied that criterion (VCRTyyFL). A valid ABPM record will have all present VCRTyyFL set to Y
VCRTyyFL	ABPM y Evaluation Result Flag	Char	Y	Character variable set to "Y" if record meets the corresponding validity criterion The values of VCRTyyFL must be the same within any combination of USUBJID, AVISIT, RECID

Additional Discussion:
Marius will provide the datasets as requested by the Agency. No further discussion is required.

Question 4a: Site 104
Does the Division agree that the steps Marius has taken to define and address this situation are appropriate?

FDA Response:
Yes. Your approach appears reasonable.

Additional Discussion:
No further discussion required.

Question 4b: Site 104
Does the Division have any additional comments or recommendations to offer regarding this situation?

FDA Response:
We note that you concluded that exposure of samples to a temperature higher than 4°C for a longer sample handling time prior to plasma preparation and freezing the plasma samples may have contributed to the observation seen at site 104. We recommend you

submit a detailed report of your assessment on how, why, and to what extent the sample handling/processing temperature and time might have affected the sample analysis outcome in your NDA.

Additional Discussion:
No further discussion required.

Question 5: Sampling Timeframe for T Determination
Does the Division agree that a single blood draw between 3-5 hrs for dose adjustment may be appropriate to support clinical dose titration decisions?

FDA Response:
Your single blood draw dose titration scheme must be based on how dose titration in your pivotal phase 3 trial was conducted. Submit the concordance analysis between the observed total testosterone C_x at each time point (i.e., 3-, 4-, and 5-hours post-dose) and total testosterone C_{avg} from your phase 3 trial.

Additional Discussion:
The FDA informed Marius that 3 to 5-hour titration window seems appropriate. Also see additional discussion under Question 6.

Question 6: Conversion of Plasma to Serum T Thresholds for Titration Using Serum Samples
Does the Division agree with our approach to establishing serum-based T thresholds to support dosing in the clinical setting?

FDA Response:
No. We do not agree. To establish serum-based testosterone concentration thresholds, you will first have to determine and propose the optimal time point for dose titration sample collection (e.g., 3-5 hours post-dose, 4 hours post-dose, etc.) based on concordance analysis (refer to our response for Question 5). Then, you need to establish a conversion factor between total testosterone concentrations measured from plasma and serum. When you derive the conversion factor, other factors such as type of test tube used for sample collection, sample collection time point (e.g., 3-, 4-, and 5-hour post-dose) and corresponding variability, sample handling temperature and time, etc. should be considered and reflected into the conversion factor as this factor would be condition/time-specific and will not be the same for across different conditions/time.

Additional Discussion:
Marius stated that regarding sample stability, analysis and establishment of a conversion factor for plasma to serum testosterone, their approach to generate a conversion factor is based on the real-world clinical practice of using serum assay for titration decisions. Marius stated that they analyzed paired plasma and serum samples from over 150 study subjects at their titration visits (samples collected at 0, 1.5, 3, 4, 5- and 6-hours post-dose). Marius did not employ a model of multiplying stability and

analytical factors to arrive at the conversion equation. For the proposed conversion equation, Marius used approximately 150 X 3 X 2 = 900 data pairs (150 subjects, samples at 3, 4, and 5-hour post-dose, and two titration visits). Marius further clarified that they did not use C_{avg} values to make titration decisions in either of their phase 3 studies. They used a clinically relevant approach of using a single T Cx value and a pre-determined titration algorithm developed by using concordance analysis to drive dose titration.

The FDA inquired as to how the substudy subjects were selected for paired plasma and serum collections. Marius explained that subject selection was based on the timing of serum substudy implementation and subject status in the continuum of study conduct, starting with the subject consent at enrollment by signing an informed consent form.

The FDA also inquired about the plasma processing times within the 110 minutes timeframe. Marius explained that there was a processing spread across that timeframe as would be expected for samples processed by 19 different clinical sites. The plasma assay has been validated for processing of samples stored in ice for a period of 110 minutes. Marius confirmed that the validation report for the plasma assay will be included with the NDA.

The FDA requested further clarification on the Bioanalytical Sample Stability Sub-study (BSSS) report. Marius stated that the BSSS results were submitted to the FDA in February 2019 (SN0035) and the BSSS report would be included in the NDA and further stated that the plasma/serum bioanalysis was validated in accordance with FDA guidelines.

The FDA requested that the Marius submit a report for the serum substudy. Marius indicated that the serum substudy analysis will be part of the clinical study report included in the NDA.

The FDA also asked Marius to provide individual PK profiles with overlaying serum and plasma PK profiles for the 0-6 hour (Visit 8E/Day 14E and Visit 10E/Day 42E) and 24-hour PK (Visit 12E/Day 90E) and Marius agreed to submit them.

The FDA inquired about the Sponsor's interpretation of a wider spread at higher concentrations in Figure 17 of the Sponsor's meeting package. The FDA requested that the Sponsor examine the plasma/serum regression plots in several different ways (including linear regression with weighting factors and nonlinear analysis) to determine the basis for variability observed at increasing T level concentrations. Marius stated that they would consider this and explore the usefulness of other regressions.

Marius indicated that they intend to submit their NDA sometime in October of 2020.

Post-meeting Comment:
In your NDA submission, we request that you include an individual level analysis/ comparison of the dose titration outcomes of serum compared to. plasma for the data that you showed in Tables 15 and 16 in your meeting package. Refer to the Table format below:

	Day 14 C_x	Titration Decision	Day 42 C_x	Titration Decision	Day 90 C_{avg}
C_3 Group Subject 01 Plasma Serum Subject 02 Plasma Serum Subject 03 Plasma Serum . . .		↑ or ↓ or ↔		↑ or ↓ or ↔	
C_4 Group Subject 04 Plasma Serum Subject 05 Plasma Serum Subject 06 Plasma Serum . . .		↑ or ↓ or ↔		↑ or ↓ or ↔	
C_5 Group Subject 07 Plasma Serum Subject 08 Plasma Serum Subject 09 Plasma Serum .		↑ or ↓ or ↔		↑ or ↓ or ↔	

. .					

Question 7: Dietary Effect
Does the Agency have any comments or questions regarding this approach?

FDA Response:
It is unclear how you define low-, normal-, and high-fat breakfast or dinner. Define this with the clinical/real life relevance in your NDA.

In addition to the data from your phase 1 food effect PK study, submit your correlation analysis between the food intake categories and the total testosterone C_{avg} and C_{max} outcome from your pivotal phase 3 trial. Also, submit the food effect analysis using fasting conditions and normal fat content as the reference group respectively. With your NDA, submit your proposal and justification/supporting information to indicate how food effect should be labeled.

Additional Discussion:
No further discussion required.

Question 8: EtOH Interaction
Does the Agency have any comment on the proposed inclusion of alcohol interaction data in the proposed package insert for SOV2012-F1?

FDA Response:
Your proposal to include the study results from the alcohol interaction assessment appears reasonable. Submit data and analysis assessing the effect of alcohol on each category of meals (e.g., high-, normal-, and low-fat meals).

Additional Discussion:
No further discussion required.

Question 9: Scope of Post-Marketing Data in the NDA

(b) (4)

FDA Response:
(b) (4) We recommend submitting all data available from real post market experience as well as from literature ((b) (4)).

Additional Discussion:
Marius proposed (b) (4) *be provided in the initial NDA submission.*

Post Meeting comment:
The Division reiterated that Marius submit all post-marketing and literature data available at the time of NDA submission.

Question 10: Pediatric Study Plan
Can the Agency provide an update on the need for, potential target population, design and timing for a pediatric study?

FDA Response:
Because your product is not a new active ingredient, new indications, new dosage forms, new dosing regimens, or new routes of administration, PREA does not apply to your application. Please see additional information under PREA REQUIREMENTS below.

Additional Discussion:
Marius stated that the FDA had incorrectly notified them about their drug product not being able to trigger PREA. Marius believes that their drug has a unique dosing regimen and therefore triggers PREA. The FDA stated that it will provide further clarification on this issue as a post meeting comment.

Post Meeting comment:
Upon further review, because the Sponsor's product is considered a new dosing regimen, PREA does apply. The Sponsor should submit their initial pediatric plan that was included in the FDA Initial Pediatric Study Plan - Written Response letter, dated February 13, 2018. Upon receipt, the pediatric plan will be formally reviewed by the PeRC committee.

Question 11: Environmental Assessment
As SOV2012-F1 will be a 505(b)(2) submission, does the Division concur that an abbreviated environmental assessment being completed by Marius is appropriate?

FDA Response:
This proposal is generally acceptable. Special disposal instructions may be needed for the product labeling.

Additional Discussion:
No further discussion required.

ADDITIONAL INFORMATION

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 EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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 iPSP, including an iPSP 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*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

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[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.
- 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 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[6]

MANUFACTURING FACILITIES

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for

[7] https://www.fda.gov/media/84223/download

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

commercial production and those used for product and manufacturing process development.

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).[9] 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 Regulations.gov.[10]

If you intend to submit a 505(b)(2) application that relies for approval 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 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. by trade name(s)).

If you intend to rely 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see

[9] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[10] http://www.regulations.gov

also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(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.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
See attached

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[11] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SURESH KAUL
08/18/2020 05:42:47 PM

IND 118675

MEETING MINUTES

Marius Pharmaceuticals, Inc.
Attention: Craig Metz, PhD
SVP, Regulatory Affairs
8601 Six Forks Road, Suite 630
Raleigh, NC 27615

Dear Dr. Metz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SOV2012-F1.

We also refer to the telecon between representatives of your firm and the FDA on April 6, 2020. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Controls for SOV2012-F1.

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

If you have any questions, call Marquita Burnett, Regulatory Business Process Manager at (240) 402-0836.

Sincerely,

{See appended electronic signature page}

Mark Seggel, PhD
Acting CMC Lead
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 6, 2020 10:00AM – 11:00AM EST
Meeting Location:	Teleconference
Application Number:	118675
Product Name:	SOV2012-F1
Indication:	Treatment of primary and secondary hypogonadism
Sponsor Name:	Marius Pharmaceuticals, Inc.
Meeting Chair:	Mark Seggel, PhD
Meeting Recorder:	LCDR Marquita Burnett, MPH

FDA ATTENDEES

Mark Seggel, PhD	CMC Lead and DP Reviewer, OPQ/ONDP/DNDPII
Yangmee Shin, PhD	Pharmacology/Toxicology Reviewer, DPT-RPURM
Kimberly Hatfield, PhD	Pharmacology/Toxicology Team Leader, DPT-RPURM
LCDR Marquita Burnett, MPH	Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES

Om Dhingra, PhD	CEO Marius Pharmaceuticals
James Bernstein, PhD	CSO Marius Pharmaceuticals
Craig Metz, PhD	Marius Pharmaceuticals SVP for Regulatory Affairs
Amit Shah	Chief Operating Officer
(b) (4)	Non-clinical (Consultant to Marius Pharmaceuticals)

1.0 BACKGROUND

On February 7, 2020, Marius Pharmaceuticals, Inc. submitted a type B meeting request. The purpose of the meeting is to discuss Chemistry, Manufacturing, and Controls for SOV2012-F1. February 20, 2020, the FDA Office of Pharmaceutical Quality (OPQ) granted a face-to-face meeting for April 6, 2020 that was converted to a teleconference on March 18, 2020.

FDA sent Preliminary Comments to Marius Pharmaceuticals, Inc.on March 30, 2020.

2. DISCUSSION

(b) (4)

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3.0 SECURE EMAIL

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ATTACHMENTS AND HANDOUTS

Preliminary comment responses included at the end of the meeting minutes

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARK R SEGGEL
04/18/2020 02:41:14 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 118675

MEETING MINUTES

SOV Therapeutics, Inc.
Attention: Craig Metz, Ph.D.
SVP Regulatory Affairs
101 Guymon Ct.
Morrisville, NC 27650

Dear Dr. Metz:

Please refer to your Pre-Investigational New Drug Application (PIND) file for testosterone undecanoate (oral).

We also refer to the meeting between representatives of your firm and the FDA on March 25, 2015. The purpose of the meeting was to discuss specific issues related to your proposed development program.

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 Jeannie Roule, Regulatory Health Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Suresh Kaul, M.D., M.P.H.
Medical Team Leader, Urology
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
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:	**Type B**
Meeting Category:	**End of Phase 2**
Meeting Date and Time:	**March 25, 2015@1:30-2:30 PM**
Meeting Location:	**White Oak Building 22, Conference Room: 1309**
Application Number:	**PIND 118675**
Product Name:	**Testosterone undecanoate (oral)**
Indication:	**Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone**
Sponsor Name:	**SOV Therapeutics, Inc.**
Meeting Chair:	**Suresh Kaul, M.D., M.P.H.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

Hylton V. Joffe, M.D., M.M.Sc.	Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Suresh Kaul, M.D., M.P.H.	Medical Team Leader
Olivia Easley, M.D.	Medical Officer Leader, DBRUP
E. Dennis Bashaw, Pharm.D.	Division Director, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology-3 (DCP-3),
Myong-Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader, OTS, OCP, DCP-3,
Chongwoo Yu, Ph.D.	Clinical Pharmacology Reviewer, OTS, OCP, DCP-3
Lynnda Reid, Ph.D.	Supervisor, Pharmacology/Toxicology, DBRUP
Yangmee Shin, Ph.D.	Pharmacology/Toxicology Reviewer, DBRUP
Mark Seggel, Ph.D.	Acting CMC Lead, DNDPII, ONDP, OPQ
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics III, OB
Vidula Kohatkar, Ph.D.	Biopharmaceutics Reviewer, OPQ
Jeannie Roule	Senior Regulatory Health Project Manager, DBRUP
Monique Falconer, M.D., M.S.	Reviewer, Division of Epidemiology II, Office of Surveillance and Epidemiology (OSE)

SPONSOR ATTENDEES

Om Dhingra, PhD	President and CEO
Craig Metz, PhD	Senior Vice President of Regulatory Affairs
[redacted] (b) (4)	
James Bernstein, PhD	Chief Scientific Officer
[redacted] (b) (4)	

QUESTIONS AND DISCUSSION

Preliminary responses were provided to the Sponsor on March 23, 2015, in response to the questions posed in the Sponsor's meeting package provided to the Division on February 24, 2015. The Sponsor's questions are presented below in **bolded** text, followed by the Division's preliminary responses in normal text.

Prior to the meeting, the Sponsor provided clarifications and several new questions that are shown below in ***bolded italics***. All additional discussion held during the meeting is summarized below in *italics.*

Question 1

(b) (4)

2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:
   a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).
   b. The in vitro dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
   c. For immediate release product the selection of the specification time point should be where Q= (b) (4) % dissolution occurs.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Also submit dissolution data for the to-be-marketed formulation (SOV2012-F1) using the final dissolution method.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

Question 2

Does the Division agree that the specifications for the phytosterol esters are appropriate for the intended use in the final drug product?

FDA Response:
While the test and acceptance criteria for phytosterol esters appear reasonable for the purpose of quality control, further assessment cannot be made until the relevant Drug Master File has been submitted and referenced. See Response to Question 4.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

Question 3

Based on the formulation development and manufacturing information provided in the Briefing Document, does the Division have any questions or comments to offer regarding its adequacy for supporting the conduct of the Phase 3 study and subsequent NDA submission?

FDA Response:
Refer to the ICH Guidance for Industry, M4Q: The CTD — Quality, August 2001 [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information /Guidances/UCM073280.pdf], and associated ICH guidances, as well as to the FDA's Pharmaceutical Quality / CMC Guidances [http://www.fda.gov/Drugs/Guidance ComplianceRegulatory Information/Guidances/ucm064979.htm] regarding documentation needed to support the proposed Phase 3 study and subsequent NDA.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

Question 4
Does the Division agree that the nonclinical research conducted by SOV and summarized above adequately addresses the Agency's pre-IND comments/questions?

FDA Response:
The adequacy of the summarized studies cannot be determined until the full data are submitted for review.

Based on the summary provided in the meeting package, the following needs to be addressed:

- Clarify the role of phytosterols in the drug product. We note high plasma concentrations and potential accumulation of the major phytosterols (i.e., [redacted] (b) (4)) in humans.
- Clarify that the phytosterols used in animal studies include all the major phytosterols. We note that the systemic exposure of [redacted] (b) (4) is greater than that of [redacted] (b) (4) in humans. You may also include plasma levels of these major phytosterols in humans through normal dietary intakes.

Additional Discussion:
Prior to the meeting, the Division reviewed the additional information included below and found it to be acceptable. At the meeting, the Division requested that copies of the references for phytosterol be submitted to the IND prior to NDA submission.

[redacted] (b) (4)

Section 3.2 of the Investigator's Brochure (included with the SOV Briefing Document) discusses in further detail the known pathways for absorption and excretion of phytosterols.

(b) (4)

Section 13.7.3.5.9 of the Briefing Document summarizes the pre-dose levels of (b) (4) ***on Day -1 and Day 84 of the Phase 2 study conducted by SOV. After 84 days, for the*** (b) (4) ***phytosterols, a slightly higher pre-dose level was measured than on Day -1 of the study. The data represent all 36 subjects of study 130210. At the conclusion of dosing in cohort 1, 18 of 21 subjects were receiving*** (b) (4) ***per day through the study medication and 3 of 21 subjects were receiving*** (b) (4) ***per day through the study medication. For cohort 2, all 15 subjects were receiving*** (b) (4) ***per day at the end of dosing.***

The animal studies (90-day dog study and male rat reproductive study) reported by SOV all used (b) (4) ***as the source of phytosterol esters.*** (b) (4) ***is also the phytosterol ester excipient used in the manufacture of the clinical SOV2012-F1 200 mg TU capsules used in the SOV Phase 2 study (Protocol 130210). The composition of*** (b) (4) ***may be found in Table 13-2 of the briefing document, which summarizes the composition of three lots of*** (b) (4)***. These compositions show that*** (b) (4)

(b) (4)

(b) (4)

(b) (4)

Question 5

Does the Division agree that, based on the currently available information, additional nonclinical research will not be required to support the conduct of the proposed Phase 3 clinical trial?

FDA Response:
Based on the information provided in the meeting package, the nonclinical program appears sufficient. However, final determination will be made pending full review of the study reports.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

Question 6

Does the Division agree that, based on the currently available information, adequate nonclinical information is available to support the submission of a reviewable NDA.

FDA Response:
Requests for additional nonclinical studies are not envisioned at this time. However, safety issues such as unexpected/significant toxicity, impurities/degradants, formulation changes, or emerging clinical safety concerns may prompt the need for additional nonclinical studies.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

Question 7

Does the Agency agree that the results from the nonclinical studies in combination with the Phase 2b study support progression to the proposed Phase 3 clinical trial?

FDA Response:
No. It is risky to progress to Phase 3 before the acceptability of the titration scheme has been confirmed and well-defined food intake instructions have been clarified.

Alcohol interaction should be assessed to determine whether co-administration with alcohol could alter the bioavailability of your product.

Additional Discussion:
The Sponsor sought further clarification regarding the Division's request for assessment of alcohol on drug interaction. The Division stated that alcohol (b) (4) *could lead to either increased or decreased exposures to testosterone undecanoate and its metabolites, depending on whether this interaction leads to increased absorption via the lymphatic system or via the portal system.*

The Sponsor inquired if the effect of alcohol could be included as part of their food effect study and the Division stated that, in principle, this may be acceptable, pending agreement on the study design.

Question 8

Does the Division agree that the proposed study to assess the normal T range for the NaF/Na_2 EDTA assay is acceptable?

FDA Response:
Yes. We remind you that your proposed bioanalytical method validation and performance should be in compliance with the Agency's Bioanalytical Method Validation Guidance *(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).*

Additional Discussion:
The Sponsor acknowledged the Division's response.

The Division added that there was lack of information in the submitted protocol synopsis for the proposed study design including the bioanalytical method; therefore, the Division is unable to make any recommendations at this time. The Sponsor acknowledged the Division's response.

Question 9

Does the Agency have any comment on the proposed titration strategy for the Proposed Phase 3 Study?

FDA Response:
Based on the limited information submitted, it is unclear how the threshold numbers of the proposed dose titration scheme (i.e., Table 15-1 on Page 144 of 381) are derived. In addition, it is unclear if a 1:1:1 randomization for sampling/titration at 3, 4, and 5 hours, respectively, is necessary. Furthermore, it is unclear from the protocol if only the first titration (day (b) (4)) will be done with this randomization or both day (b) (4) and day (b) (4) dose titrations are going to be randomized for titration based on 3, 4, or 5 hour sample.

Your Phase 3 study should demonstrate that the proposed dose regimen using the proposed titration scheme achieves the agreed upon efficacy success thresholds. The proposed Phase 3 protocol should pre-specify the means of dose titration - the study protocol could employ the proposed titration scheme based upon a single blood draw, or you could base the titration on the 24-hour total testosterone C_{avg} with pre-specified methodology stipulated for subsequent correlation to a single timepoint.

Sponsor's Response to FDA's Preliminary Comments:

(b) (4)

Additional Discussion:

(b) (4)

Question 10

Does the Agency have any comments on the proposed safety-monitoring framework?

FDA Response:

1. Testosterone undecanoate (TU), dihydrotestosterone undecanoate (DHTU) and estradiol should be measured in all subjects; results from a 28-subject subset may not be representative of the entire study population.

Additional Discussion:

The Sponsor stated that they agree to measure TU, DHTU, and estradiol in all subjects.

2. Confirm that subjects with serum testosterone outside the therapeutic range during the safety extension (i.e. at days 180 and 270) will have their dose titrated so that they are not committed to an incorrect dose for the duration of the study. You should continue to monitor the total testosterone concentrations on Days 180 and 270

Additional Discussion:

The Sponsor confirmed that plasma testosterone will be measured on Days 180 and 270, and the dose of TU will be adjusted if necessary.

3. Provide justification for the proposed free testosterone calculation method. Because of the apparent effects of your product on sex hormone binding globulin (SHBG), it will be important to show that your product also achieves free testosterone concentrations within the normal range.

Additional Discussion:
The Sponsor stated that they are aware of the challenges inherent in both direct and calculated measurements of free testosterone and will provide justification for the method of calculating or measuring free testosterone in the protocol.

The Division clarified that they have no preferred method and only request that the Sponsor use a valid method that is adequately justified.

4. Confirm that you anticipate at least 100 patients to complete 12 months of therapy. It is possible that additional long-term safety data will be needed based on any signals that become apparent during the clinical development program.

Additional Discussion:
The Sponsor confirmed that at least 100 patients will complete 12 months of therapy and that they will use Androgel as an active comparator.

The Division stated that collecting PK profiles would be appropriate in the Androgel comparator arm. In addition the Division agreed that 100 subjects in the Androgel comparator arm would be acceptable.

5. The effect of your product on cardiovascular parameters such as blood pressure and serum LDL and HDL will be an important review issue.

6. Phase 2 data show that exposure to TU and DHTU far exceed exposures to testosterone (T) and DHT. You should address whether exposures to TU or DHTU could have any potential clinical ramifications.

Additional Discussion:
The Sponsor does not believe that TU and DHTU have activity at the androgen receptor, nor do they believe that large quantities of TU/DHTU in serum will displace T or DHT from the receptor. They believe that comparing androgenic effects of TU to Androgel (active comparator) in the clinical trial will help determine whether TU/DHTU are pharmacologically active (i.e. if there is excess androgenicity in the TU arm relative to Androgel, it would suggest that TU/DHTU have activity at androgen receptor). This would be supportive provided that their product and Androgel achieve comparable exposures to testosterone and DHT.

7. We remind you that the goal of testosterone replacement therapy is to reliably and consistently replace testosterone and its critical metabolites (e.g., dihydrotestosterone and estradiol) to within the normal range. If your product does not do this, you will need to address why you consider your product to be testosterone replacement therapy.

Question 11

(b) (4)

Does this approach seem reasonable to the Agency?

FDA Response:
No. The primary efficacy analysis should be based on all subjects who take at least one dose of the study drug. For the primary analysis, we suggest a model-based imputation method for the endpoint missing PK data. (b) (4)

Additional Discussion:
The Sponsor inquired about issues regarding selection of the optimal imputation method for missing PK data.

The Division recommended that the Sponsor should include all subjects who are exposed to at least one dose of study drug for the analysis of the primary outcome and the Sponsor agreed.

For subjects with no post-baseline data, the Division recommends that these subjects will be considered failure in the analysis. The Division clarified that they have no specific recommendations as to an appropriate modeling approach prior to study completion, but regression modeling (including multiple imputation) can be used to predict missing PK data using the available information. The Sponsor should include written justification of the modeling approach selected in the full Phase 3 protocol which the Division will review. The method should account for the different reasons why subjects may discontinue prematurely (e.g., due to safety or tolerability issues). Baseline demographic information should be used in the multiple imputation model.

The Sponsor stated that as part of the Phase 3 program it would provide detailed subject narratives for all subject discontinuations due to safety or tolerability issues.

The Division stated that it will provide a useful reference pertaining to missing data in clinical trials as a post meeting comment in the meeting minutes.

Post-Meeting Comment:
"The Prevention and Treatment of Missing Data in Clinical Trials", National Research Council of the National Academics, 2010.
http://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials

Question 12

Does the Division concur that, based on currently available information, the design of the proposed Phase 3 study will be adequate to support the submission of a reviewable NDA.

FDA Response:

No. We have the following comments regarding the Phase 3 study design:

1. Food intake instructions: You propose to assign enrolled subjects to low fat, normal fat or high fat meals based on the assessment of the individual's diet survey. We remind you that the food intake instruction for Phase 3 development needs to be realistic for patient compliance and labeling. We recommend that the food intake instructions should be under fasting or under fed condition without any further restrictions regarding the fat content of the meal. In addition, we recommend that you conduct a "timed food effect clinical study" that could be used to design dosing recommendations with regard to meals that would be more practical (i.e., reproducible) with unsupervised use. Such a study could utilize a fasted treatment cohort and treatment cohorts where a single dose is administered at different time points before and after a standardized meal. This timed food effect study could be helpful in developing dosing instructions (i.e., timing) of the evening dose in relation to dinner to minimize the impact of food effect down to an acceptable level. In summary, you should have a well-defined food intake instruction for your product before proceeding to Phase 3.

Additional Discussion:

(b) (4)

2. The entry criteria:
   - Both baseline morning total T concentrations should be less than 300 ng/dL. These two measurements should be obtained on separate mornings at least 3 days apart
   - There should not be any restriction regarding body mass index (BMI) for enrollment

Additional discussion:
The Sponsor agreed to these recommendations.

3. Confirm that the proposed normal T concentration range is 300-1,000 ng/dL

Additional discussion:

(b) (4)

4. In the absence of an approved oral TU product in the U.S., we recommend that you use an approved U.S. testosterone product indicated for male hypogonadism as a comparator arm for safety.

Additional discussion: (b) (4)

Discussion of your NDA submission is premature at this stage of development.

Question 13

In accordance with FDA Guidance for Special Protocol Assessment (May 2002), SOV is considering the submission of a Special Protocol Assessment Request following receipt of the official minutes from the End of Phase 2 meeting. Does the Division have any comment/advice to offer on an SPA submission for this development program?

FDA Response:
If you choose to submit a Special Protocol Assessment (SPA), we encourage you to first address all outstanding issues discussed in our previous responses.

Additional Discussion:
The Sponsor acknowledged the Division's response. There was no additional discussion.

ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (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.

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.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.

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

/s/

SURESH KAUL
04/24/2015