CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208088Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 106476

MEETING MINUTES

Lipocine Incorporated
Attention: Satish K. Nachaegari
Associate Director, Regulatory and Clinical Affairs
675 Arapeen Drive, Suite 202
Salt Lake City, UT 84108

Dear Mr. Nachaegari:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LPCN 1021 (testosterone undecanoate capsules).

We also refer to the meeting between representatives of your firm and the FDA on March 19, 2015. The purpose of the meeting was to discuss your planned NDA submission.

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:	**Pre-NDA**
Meeting Date and Time:	**March 19, 2015 @ 11:30 AM to 1:00 PM**
Meeting Location:	**White Oak Building 22, Conference Room: 1311**
Application Number:	**106476**
Product Name;	**LPCN 1021 (testosterone undecanoate capsules)**
Indication:	**Testosterone replacement therapy in adult males**
Sponsor Name:	**Lipocine Incorporated**
Meeting Chair:	**Suresh Kaul, M.D., M.P.H.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES

Hylton 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, DBRUP
Martin Kaufman, D.P.M., M.B.A.	Clinical Analyst, DBRUP
Lynnda Reid, Ph.D.	Supervisor, Pharmacology/Toxicology, DBRUP
Yangmee Shin, Ph.D.	Pharmacology/Toxicology Reviewer, DBRUP
Myong-Jin Kim, Pharm.D.	Clinical Pharmacology Team Leader, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology-3 (DCP-3)
LaiMing Lee, Ph.D.	Clinical Pharmacology Reviewer, OTS, OCP, DCP-3
Dhananjay D. Marathe, Ph.D.	Pharmacometrics Reviewer, OTS, OCP, Division of Pharmacometrics (DPM)
Mark Seggel, Ph.D.	Acting CMC Lead, DNDPII, ONDP, OPQ
Hitesh Shroff, Ph.D.	CMC Reviewer, DNDPII, ONDP, OPQ OPS
Mahboob Sobhan, Ph.D.	Statistical Team Leader, Division of Biometrics (DB) III, OTS
Weiya Zhang, Ph.D.	Statistical Reviewer, DBIII, OTS
Kelly Kitchens, Ph.D.	Acting Biopharmaceutics Quality Assessment Lead, OPQ
Vidula Kolhatkar, Ph.D.	Biopharmaceutics Reviewer, OPQ
Jeannie Roule	Regulatory Health Project Manager, DBRUP

SPONSOR ATTENDEES

Mahesh Patel, Ph.D.	President & Chief Executive Officer
Nachiappan Chidambaram, Ph.D.	Vice President, Product Development

Anthony DelConte, MD	Chief Medical Director
Satish Nachaegari, MS	Associate Director, Regulatory and Clinical Affairs
Burke Byrne, MBA	Manager, Regulatory and Clinical Affairs
(b) (4)	Consultant

QUESTIONS AND DISCUSSION
Preliminary responses were provided to the Sponsor on March 18, 2015, in response to the questions posed in the Sponsor's meeting package provided to the Division on February 18, 2015. The Sponsor's questions are presented below in **bolded** text, followed by the Division's preliminary responses in normal text. Additional discussion held during the meeting is summarized below in *italics.*

QUESTIONS AND DISCUSSION

General Comment: Currently, the effect of meals with high and low fat content on the absorption of LPCN 1021 is unknown. If changes in fat content have considerable impact on exposures to your product/metabolites, we may question the interpretability of your phase 3 study results and applicability of those results to the real-world setting because it is unreasonable to expect patients to be able to maintain consistency of fat content with every breakfast and every dinner while taking this chronic medication. We strongly recommend that you submit preliminary results of Study LPCN 1020-14-001 (food effect study) for FDA review and comment prior to submission of your NDA.

Additional Discussion:
The Division requested an update and more details concerning the Sponsor's food effect study because the Division has concerns regarding how the results of the study would translate into labeling and whether the results could impact interpretability of the phase 3 data. The Division inquired about the specific diet patients received on the designated pharmacokinetic (PK) days during the phase 3 study and whether this diet was representative of the diet patients followed on all of the other days of the study.

The Sponsor stated that their food effect study is scheduled to start dosing next week. The Sponsor also stated that during their phase 3 study, patients were encouraged to consume a standard meal with a fat content between 20 and 35% and a caloric content between 800 and 1400 kcal. Patients had a choice of 300 different standardized meals that were representative of a normal American diet. The food effect study will include high fat, low fat, and fasted arms, in addition to an arm with the standard 20 -35% fat content meal.

The Division noted that labeled food intake instructions typically state to take the product under fasting or under fed condition (whichever is appropriate and supported by data) without any further restrictions regarding the fat content of the meal, because it is not reasonable to expect patients to know the fat content from meal to meal. In addition, the Division suggested modifying the food effect study to include a "timed food effect" assessment (e.g., also dosing the subjects at 0.5, 1,and 2 hours post meal) that could be used to inform on PK exposures with dosing after meals. The Division recommended that the Sponsor submit the results of the food effect study for

FDA review and comment before they submit their NDA. The Division stressed that food effect is a critical issue and we do not yet have sufficient information to determine the extent of the food effect and the impact that food effect could have on interpretability of the phase 3 study results. In addition to the results from this food effect study, the Division also requested details of the meals (including the fat content) that were given in the phase 3 study on PK days, as well as what patients were instructed to do about meals on other days in the phase 3 study. The Sponsor agreed.

Pharmacology/Toxicology

Question #1

Based on the nonclinical program performed by Lipocine, and literature information on T carcinogenicity and embryo fetal toxicity, Lipocine believes that the nonclinical package is sufficient to support NDA filing and approval. The content of the nonclinical toxicology (carcinogenesis, mutagenesis, impairment of fertility) section of the labeling will be in alignment with the labeling of other TRT products.

Does the Division continue to agree that no additional nonclinical characterization of LPCN 1021 is required for NDA filing?

FDA Response:

Yes. We do not anticipate the need for additional nonclinical studies unless there are certain circumstances such as unexpected/significant toxicity, new impurities, formulation changes, or emerging clinical safety concerns.

Additional Discussion:

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

Question #2

Lipocine considers that the degradation products are sufficiently characterized and qualified to support NDA filing and approval.

Does the Division agree that the degradation products have been sufficiently characterized and qualified to support NDA filing and approval?

FDA Response:

We concur that the specified degradation products have been adequately characterized assuming that, 1) the impurities are typically seen at < (b) (4)% as described in the package; 2) the level of the (b) (4) is within the qualification threshold for the proposed ascorbyl palmitate-containing formulation; and 3) the drug substance for the to-be-marketed formulation is provided by (b) (4)

Be aware that additional nonclinical data might be needed to qualify any other impurities detected above the reporting limits during stability studies. In your NDA, provide a side-by-side

comparison of each impurity for the drug substance and drug product used in nonclinical and clinical studies versus the proposed formulation.

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

Clinical Program: Safety / Efficacy
Question #3
The primary efficacy endpoints data confirm that LPCN 1021 has met the efficacy requirements for a TRT, and reliably restores T to normal levels.
Does the Division agree that LPCN 1021 meets the pre-specified primary efficacy end point requirements for a TRT?

FDA Response:
No. With the limited data provided in the meeting package, LPCN-1021 appears to have met the pre-specified primary endpoint of ≥75% (lower bound of the 95% confidence interval ≥ 65%) of subjects having Cavg of serum total T within the normal range at Week 13. However, more details on the dropout rate of 25% in the LPCN-1021 group (twice higher than the Androgel 1.62% at Week 13) would be needed to justify the appropriateness of the sensitivity analyses provided. All available information for discontinued patients, including case report forms, should be included in the NDA submission.

In addition, the proportion of subjects with T-Cmax>2500 ng/dL, as one of key secondary endpoints, should also be met as a part of the requirement for the TRT class. As per your brief summary of the phase 3 trial results, eight subjects have Cmax>2500 ng/dL with the dosage and titration regimen used in the study. Include detailed information about these outliers in your NDA. The adequacy of the findings will be a review issue.

Decisions regarding efficacy will be made after a complete review of the data during the NDA review and will be based on the totality of information including, but not limited to, the primary efficacy endpoint and the key secondary endpoints.

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

See our General Comment above pertaining to food effect.

Additional Discussion:
The Sponsor sought further clarification regarding the Division's request for the assessment of alcohol on drug absorption. The Division stated that alcohol could affect the solubility of the drug, which 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 asked if they can address the division's concern using data from in vitro dissolution studies in the presence of alcohol. The Division responded that this requires further internal discussion and a response will be provided as a post-meeting comment.

The Division noted that the phase 3 study had a high dropout rate and stated that the Sponsor will need to provide in the NDA a detailed explanation and justification for the dropouts.

The Division also noted that there were eight subjects with Cmax greater than 2500 ng/dL at Week 13. The Division reiterated that the number of subjects with Cmax greater than 2500 ng/dL in the study is a concern and will be a review issue during the NDA. The Sponsor explained that subjects with Cmax greater than 2500 ng/dL had erratic T levels even before they started treatment. The Sponsor stated that they are investigating further to see if there was a large variation in the DHT value as well. They further explained that the particular site where the T levels were drawn, did not always follow the protocol-specified titration schedule and that this might have contributed to these findings. The Division requested that the Sponsor include detailed information on the outliers in the NDA.

The Division stated that in the meeting package the Sponsor provided very little data for DHT, the DHT/T ratio and estradiol values for Weeks 3, 7 and 13 and requested that detailed information be included in the NDA. The Sponsor agreed.

Post-Meeting Comment:
The Sponsor can attempt to address the Division's concern about an interaction with alcohol by using an in vitro dissolution study. The Sponsor may submit the proposed study plan and justification to the Agency prior to conducting the study and a response on the adequacy of the in-vitro alcohol-interaction study design will be provided in due time. Whether an in vivo alcohol interaction study is needed will depend on the results of the in vitro study.

Safety
Question #4
Does the Division agree that the safety data presented in this package along with the 52 week safety data will be sufficient to characterize the overall safety of LPCN 1021?

FDA Response:
Based on the safety database of nine clinical trials, it appears that you meet the safety criteria outlined in the ICH E1A Guidance. However, it is premature for the Division to agree that no additional safety data will be required before a thorough review of the NDA. The adequacy of the safety data will depend on the number of patients who complete the trial with one year of exposure to the drug. Details on handling of missing safety parameters will also be needed.

We also note that the meeting package did not contain information on DHT concentrations and the DHT/T ratio at Weeks 3, 7, and 13. This information should be included in the NDA. In addition, it is unclear why you are focusing only on DHT concentrations and DHT/T ratios obtained 3-6 hours post morning dosing, and whether this window is appropriate for comparisons

to Androgel. Your NDA should also assess DHT, the DHT/T ratio and estradiol over the entire 24-hour period following dosing (e.g., using Cavg, Cmax) to provide a more integrated assessment of exposures. If your product is to be considered replacement therapy, the expectation is that it will restore testosterone and its critical metabolites (e.g,. DHT, estradiol) to the normal range.

Additional Discussion:
The Division remarked that if the Sponsor's product pushed patients into a higher range for estradiol or DHT, then the Division would question whether these findings are consistent with testosterone replacement therapy (TRT), which has the goal of restoring testosterone and its critical metabolites to the normal range. The Division expects that after titration is completed and the subject is at "goal" for testosterone, the subject should be at "goal" for the testosterone metabolites as well.

The Division also noted that the product causes a reduction in SHBG, which could impact free testosterone concentrations. The NDA should include detailed information on free testosterone concentrations achieved with LCPN, including the method used to calculate/measure free testosterone.

The Division also requested that the Sponsor explain why they selected a window of 3-6 hours post AM dose for DHT, DHT/T ratios, and estradiol monitoring and whether that time frame is a true representation of overall exposure to DHT and estradiol during the dosing interval. The Sponsor stated that they have a full PK profile for the LPCN arm, but not for the Androgel arm and will submit detailed justification about the selection of the time points in the NDA. Regardless, the Division requested that the NDA also include analyses of DHT, DHT/T and estradiol that uses data from the full PK profile for these hormones.

The Division expressed concern about interpreting safety comparisons to Androgel without knowing whether subjects in the Androgel group had similar overall exposures to testosterone and its metabolites as those treated with LCPN.

The Division also inquired as to what the reference ranges were for DHT and the DHT/T ratio for their specific assay and the laboratory. The Sponsor stated that the laboratory that they used to measure DHT did not have a reference (normal) range, but used a validated method. The Sponsor will submit details about the methodology with the NDA. Again, the Division's expectation for testosterone replacement therapy is restoration of testosterone and its critical metabolites to the normal range.

Clinical Use Titration Approach

Question #5

Does the Division agree that the proposed approach is reasonable [redacted] recommendations for titration of the LPCN 1021 product?

FDA Response:

Demonstration of efficacy in your phase 3 study at Week 13 included titrations based upon a 24-hour evaluation of Cavg at Weeks 3 and 7; however, your proposal for dose adjustment for clinical practice will be based on a single testosterone concentration drawn between 3 to 6 hours after the morning dose. In your NDA, we recommend you assess the correlation of 24-hr total testosterone Cavg to the testosterone concentration at 3, 4, 5 and 6 hours post-dose at Week 13. Depending on the strength of these correlations, we will determine whether one or more of these timepoints are appropriate for titrating your product in clinical practice. Additionally, your phase 3 titration scheme included Cmax (reduce dose if Cmax is greater 1500 ng/dL irrespective of Cavg). Clarify how your [redacted] dose instruction, which does not include a Cmax consideration, would correlate to the demonstration of efficacy in your phase 3 trial using Cavg. It appears that the testosterone concentrations used for the clinical titration may be different from the testosterone concentrations used for titrations in your Phase 3 trial; clarify how you plan to support deviations from the phase 3 study design.

You have proposed [redacted] dose strengths – [redacted] 112.5 mg tablets. [redacted]

Additional Discussion:

The Division stated that the Sponsor's titration scheme used in the Phase 3 study included both Cmax and Cavg. The Division inquired about the number of subjects titrated on Cmax alone and on Cavg alone. The Division expressed concerns that the proposed titration [redacted] using a single time point that will be correlated to Cavg does not reflect the titration scheme used in the completed Phase 3 study that included both Cavg and Cmax.

The Sponsor stated that a subject was up-titrated if the 24-hour Cavg was less than 300 ng/dL, remained on the same dose if 24-hour Cavg was between 300 and 1140 ng/dL, or down-titrated if the 24-hour Cavg was above 1140 ng/dL. Cmax was generally used for down titration. Cmax was used for down titration if the T value was greater than 1500 ng/dL regardless of the Cavg value. The Sponsor stated that patients who were down-titrated due to a Cmax greater than 1500 ng/dL also had a Cavg above 1140 ng/dL. The Sponsor confirmed that they will submit justification and a correlation between Cmax and Cavg in the NDA.

The Division further inquired as to how the Sponsor selected the (b) (4) *hour time point. The Sponsor responded that this time point was based on the phase 2 and 3 data and that this time point is very close to Cmax. The Sponsor will submit this information in the NDA.*

The Division remarked that if the down titration was based on Cmax it is possible that some subjects could erroneously not be down titrated in clinical practice if the suggested single time point used for titration is not able to mimic or translate effectively the titration rules employed in the trial. It is important to show that the titration rule (b) (4) *would translate to similar titration steps as occurred in the phase 3 study. This will be an important review issue.*

The Division inquired about the use of the 112.5 mg dosage strength in previous studies. The Sponsor clarified that the 112.5 mg tablet was only used in the Phase 3 Study LPCN 1021-13-001. (b) (4) *The Division stated that it may be a reasonable approach and recommended the Sponsor provide the details of their plan and an appropriate justification.*

Clinical Program- Labeling Studies
Question #6
Does Division agree with Lipocine's planned approach for the food effect labeling?

FDA Response:
It is premature to comment until the Division has reviewed the final results of the food study report. The effect of food should be evaluated relative to the predefined range for efficacy (e.g. serum total testosterone range of 300 – 1140 ng/dL). Deviations from the predefined range due to food may result in loss of efficacy or safety concerns. We will review the results from both the food effect study and the phase 3 trial (meal vs. Cmax and Cavg) before determining the adequacy of the proposed labeling "taken with a meal" "without specifying fat content in the label." See our General Comment above.

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

Target Product Profile (TPP):
Question #7
Does the Division agree with the proposed product label language and sources of information?

FDA Response:
The overall profile of your proposed labeling appears reasonable. However, the adequacy of the content and language will be determined after our review of the data submitted in the NDA.
In addition, your label will need to include all current language that is relevant to class labeling.

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

Pharmacokinetic Studies in Special Population:
Question #8
Does the Division agree that renal and hepatic impairment PK studies are not required for the NDA submission?

FDA Response:
Yes. We agree that renal and hepatic impairment PK studies are not required for the NDA submission.

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

Drug-drug interactions (DDI)
Question #9
Given that other TRT products share the same instructions for DDI (noting insulin, oral anticoagulants, and corticosteroids), Lipocine plans to use the TRT product class DDI instructions in the LPCN 1021 proposed labeling.
Does the Division agree that this plan is acceptable?

FDA Response:
Yes. We agree that drug-drug interaction in the target population can be addressed by literature and overall safety profile. However, if any potential DDI signal is raised during the NDA review, more data may be needed.

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

Procedural
Question #10
Does the Division agree that the LPCN 1021 NDA qualifies for Priority Review?

FDA Response:
Decisions regarding priority review designations are made at filing. A priority review designation is assigned to applications for drugs that treat serious conditions and provide

significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to available therapies. It is unlikely that your NDA will qualify for a priority review given the wide range of available testosterone products.

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

Question #11
Does the Division concur with review of CMC and nonclinical sections 90 days prior to NDA submission?

FDA Response:
In accordance with 21 CFR 314.50(d)(1)(iv), Lipocine may submit a complete chemistry, manufacturing, and controls section 90 days prior to NDA submission. However, keep in mind that the FDA will review such early submissions as resources permit.

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

Question #12
Does the Division deem the detailed listing of the sections of eCTD submission sufficient for acceptance of NDA filing?

FDA Response:
No. See responses to Questions 2 and 13. Section 5.3.5.3 should be included.

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

Integrated Summaries
Question #13
Does the division agree that ISS and ISE are not required for this NDA?

FDA Response:
No. The safety data should be integrated as ISS based on single-dose vs. multiple-dose studies in hypogonadal males.

Additional Discussion:
The Sponsor stated that they do not think an ISS is necessary because their development program is small. The Sponsor intends to submit a waiver for an ISS, and the Division agreed.

The Sponsor inquired as to how they should pool together all of their studies such as single dose vs. multiple dose studies. The Division remarked that we would provide a response as a post-meeting comment.

Post-Meeting comment:
In the ISS, safety data from the five phase 1 studies conducted in hypogonadal men (Studies LPCN 1021-09-001, S361.1.001, M12-778, M13-298, and 1021-14-001) should be pooled. Safety data from the other studies, including the phase 3 study (1021-14-001) should be presented separately.

Risk Evaluation and Mitigation Strategy (REMS)
Question #14
Does the Division agree that LPCN 1021 does not need a specific REMS package to be submitted in the NDA?

FDA Response:
Yes. However, we will require a REMS after NDA submission if the need for any element of a REMS is identified during the NDA review.

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

Environmental Assessment
Question #15
Does the Division agree that the product qualifies for exclusion from requiring environmental assessment?

FDA Response:
The product appears to qualify for a categorical exclusion under 21 CFR 25.31(b), based on the expected introduction concentration (EIC) calculated in Appendix 14 of the applicant's Type B, Pre-NDA Meeting Briefing Package, and the scientific literature. The product does not, however, appear to qualify for a categorical exclusion under 21 CFR 25.31(c), due to the lack of data to substantiate the claim.

Regarding 21 CFR 25.31(b), your estimated introductory concentration (EIC) is less than the 1 ppb categorical exclusion level. Published literature, however, indicates that this product has the potential for harm to the environment at EICs less than 1 ppb,[1] which could constitute an "extraordinary circumstance" if available data establish that, at the expected level of exposure, there is potential for serious harm to the environment (21 CFR 25.21(a)). Nevertheless, your calculated EIC appears to be significantly lower than relevant predicted no effect concentrations

[1] For example, see Section II.C (pp. 7-13) of USFDA, 2013, "Response to Citizen Petition to the FDA Commissioner under the National Environmental Policy Act and Administrative Procedure Act Requesting an Amendment to an FDA Rule Regarding Human Drugs and Biologics," Docket No. FDA-2010-P-0377.

(PNECs) in the literature.[2] Provide a brief review of the relevant literature or other data to substantiate the claim for a categorical exclusion under 21 CFR 25.31(b). Also, a statement regarding extraordinary circumstances must accompany a claim for categorical exclusion, per 21 CFR 25.15(a).

Regarding 21 CFR 25.31(c), because of the concern for extraordinary circumstances noted above, supporting data would need to be provided to support a claim that this action would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

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

Controlled Substance Scheduling
Question #16
Given that the active ingredients are already present in approved drug products in the US, Lipocine believes that the LPCN 1021 NDA does not require assessment of DEA scheduling or abuse potential and the approved product label language related to abuse and dependence can be used in LPCN 1021 product label.
Does the Division agree that LPCN 1021 does not require assessment of abuse or DEA scheduling and that label language consistent with other approved products would be sufficient?

FDA Response:
Yes. Your product will not require further assessment of the abuse potential or DEA scheduling. Because your product contains testosterone and testosterone is a Schedule III controlled substance in the Controlled Substances Act, your Prescribing Information (PI) will need to include class labeling pertaining to the Schedule, similar to other already approved testosterone products.

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

Chemistry, Manufacturing and Controls (CMC)
Question #17
Does the Division agree that the proposed specifications for the commercial product are acceptable?

[2] For example, see Khan, U. and Nicell, J. (2010), "Assessment of the Aquatic Release and Relevance of Selected Endogenous Chemicals: Androgens, Thyroids and Their in Vivo Metabolites," *Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations*, R. U. Halden. Washington, DC, American Chemical Society: 437-468.

FDA Response:
The drug product specification should include a second identification test. The test for impurities should include limits for testosterone and [redacted] (b) (4), as well as a limit for Total Impurities. Acceptance criteria for the three specified degradation products will be based on levels qualified in toxicology studies as well as process capability and product stability data.

Tests and acceptance criteria for [redacted] (b) (4) assay, [redacted] (b) (4) and microbial limits should not be omitted from the drug product specification.

Refer to ICH Q6A, Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Drug Products: Chemical Substances, December 2000.

The acceptability of the proposed dissolution specification for your product will be made during the NDA review process based on the totality of the provided dissolution data. Also refer to the comments in response to question #21 for our recommendations on the development of your proposed dissolution method and specification.

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

Question #18
Based on the rationale provided for [redacted] (b) (4) in Table 31, does the Division agree that testing of [redacted] (b) (4) as part of the drug product testing is not necessary?

FDA Response:
No. See response to Question 17.

Additional Discussion:
[redacted] (b) (4)

Question #19
Does the Division agree that the information presented in the CMC package adequately supports filing and approval of LPCN 1021 NDA?

FDA Response:
The application is expected to be complete at the time of submission. As noted in the November 15, 2012 meeting minutes, "additional stability data on the primary stability batches would be

accepted up to the first 30 days of the review cycle. During the NDA review, expiry will be based on evaluation of the submitted data and any additional supporting data, i.e., stability data provided on earlier formulations."

Drug product stability testing should include freeze-thaw temperature cycling and photostability testing.

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

General

Question #21

Does the Division agree that the NDA package as described in this Briefing Package is sufficient for NDA submission?

FDA Response:

No. As mentioned previously, we recommend that you submit your findings from the ongoing food effect study for FDA review and comment prior to NDA submission.

You should also include the analyses of effect of body weight/body mass index (BMI) on $C_{avg(0-24h)}$ and C_{max} to explore whether a lower starting dose in patients with lower body weight/BMI

(e.g. < 80 kg) would impact the incidence of titrations needed to achieve the target testosterone concentration range.

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

Other Comments:

A. Clarify whether you have any efficacy data from the Androgel comparator arm in your phase 3 trial.

B. Include justification in your NDA for why the high TU and DHTU concentrations do not raise clinical concerns.

C. Because your product reduces SHBG, it will be important to show that free testosterone concentrations are within the normal range. Provide sufficient justification in your NDA to support the method you have used for measuring/calculating free testosterone.

D. We have the following comments regarding the dissolution information that should be provided in your NDA.

1. **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
   a. Solubility data for the drug substance covering the pH range.
   b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.
   c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).
   d. Data to support the discriminating ability of the selected dissolution method. In general, the tests conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables).

e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

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.

Additional Discussion:
Regarding the dissolution method, the Division suggested that the Sponsor review FDA recommendations and consider exploring (b) (4)*, because the proposed dissolution method includes the use of* (b) (4) *The Division reiterated that the complete dissolution method development report should be provided in the NDA submission and should include justification for the proposed dissolution method conditions. The Sponsor replied that they will take the Division's recommendations into consideration.*

ADDITIONAL DISCUSSION:
This Additional Discussion below was not presented in the Sponsor's Briefing package:
*On March 18, 2015, the Sponsor submitted two additional questions via email (see **bolded** text below) that they hoped would be addressed during the meeting on March 19, 2015.*

Submitted on March 18, 2015:
The Sponsor stated, that following the submission of the pre-NDA briefing package, FDA announced a drug safety communication, dated March 3rd 2015, related to testosterone replacement therapy (TRT). We would like to request the Division to consider the following questions for discussion and provide guidance in our Pre NDA meeting in addition to the questions submitted in our briefing package.
In the drug safety communication related to TRT products dated March 3rd 2015, the Agency noted requiring conduct of a study as below:

"We are also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. We are encouraging these manufacturers to work together on a clinical trial, but they are allowed to work separately if they so choose."

Lipocine is seeking a TRT indication for LPCN 1021, consistent with other approved TRT products. We would like to seek Division's clarification on the following questions in our Pre NDA meeting:

1. ***It is our understanding that the above study is not required to be conducted pre-approval, do you agree?***

2. ***Does the Division agree that a new oral product will be considered similar to other TRT products in relation to the above referenced study?***

Additional Discussion:
The Division stated that if the Sponsor's CV profile for their product is in line with the other approved testosterone products and there are no unexpected CV concerns in the NDA, then a CV study would not be required prior to approval. However, a CV study would be required post-approval, as we are requiring with the approved testosterone replacement therapies. The Division clarified that this requirement is for a controlled clinical trial that accesses CV outcomes and that an epidemiological study would not be adequate to address this requirement.

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 held on or after November 6, 2012. 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 Pediatric and Maternal Health Staff 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. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.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

MANUFACTURING FACILITIES

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.				

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. 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 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. 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 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.

INSPECTION INFORMATION:

(Non-Manufacturing)

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

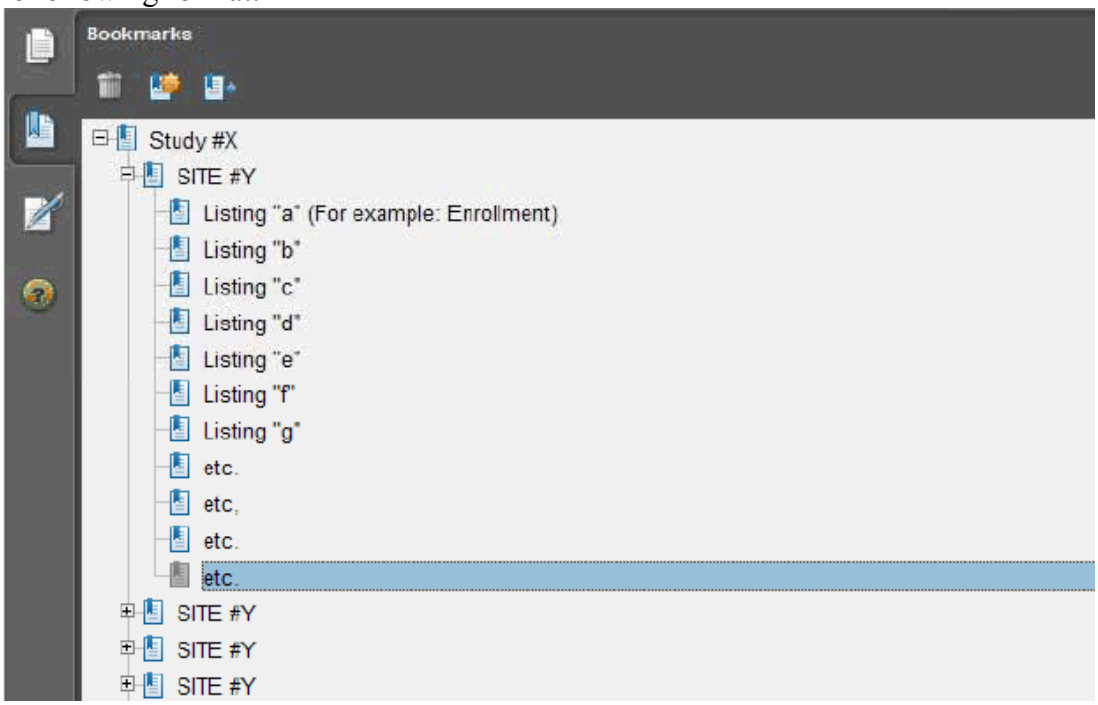
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[3]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[3] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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
04/17/2015