CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078104

MEETING MINUTES

Clarus Therapeutics, Inc.
Attention: Robert E. Dudley, Ph.D.
President and CEO
500 Skokie Blvd., Suite 250
Northbrook, IL 60062

Dear Dr. Dudley:

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

We also refer to the meeting between representatives of your firm and the FDA on October 8, 2013. The purpose of the meeting was to obtain concurrence on your plan for your 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 Project Manager at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type B**
Meeting Category:	**Pre-NDA**
Meeting Date and Time:	**October 8, 2013 @10-11:00 AM**
Meeting Location:	**White Oak Building 22, Conference Room: 1421**
Application Number:	**IND 078104**
Product Name:	**Oral testosterone undecanoate**
Indication:	**Testosterone replacement therapy**
Sponsor/Applicant Name:	**Clarus Therapeutics, Inc**
Meeting Chair:	**Mark Hirsch**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES:

Hylton Joffe, M.D., M.M.Sc.	Director, Division of Bone, Reproductive, and Urologic Products (DBRUP)
Mark Hirsch, M.D.	Medical Team Leader, DBRUP
Jin Chen, M.D.	Medical Officer, DBRUP
Harry Handelsman, D.O.	Medical Officer, DBRUP
Eric Andreasen, Ph.D.	Pharmacology/Toxicology Reviewer, DBRUP
Myong-Jin Kim, Pharm. D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology-3 (DCP-3), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
LaiMing Lee, Ph.D.	Clinical Pharmacology Reviewer, DCP-3, OCP, OTS
Mahbob Sobhan, Ph.D.	Team Leader, Division of Biometrics III, Office of Biostatistics, OTS
Donna Christner, Ph.D.	CMC Lead, Division of New Drug Quality Assessment II, Office of New Drug Quality Assessment (ONDQA), Office of Pharmaceutical Sciences (OPS)
Gene Holbert, Ph.D.	CMC Reviewer, Division of New Drug Quality Assessment II, ONDQA, OPS
Yaning Wang, Ph.D.	Pharmacometrics Team Leader, Division of Pharmacometrics (DPM), OCP, OTS
Jee Eun Lee, Ph.D.	Pharmacometrics Reviewer, DPM, OCP, OTS
Tapash Ghosh, Ph.D.	Biopharmaceutics Team Leader, ONDQA
Kelly M. Kitchens, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Raanan Bloom, Ph.D.	Toxicologist, OPS, Immediate Office (IO)
James Laurenson, MS	Toxicologist/Environmental Officer, Office of Pharmaceutical Science, Immediate Office, Environmental Assessment Team
Jennifer Mercier	Chief, Project Management Staff, DBRUP
Jeannie Roule	Regulatory Health Project Manager, DBRUP
Maria Walsh, RN, MS,	Associate Director for Regulatory Affairs
Richard Moscicki, M.D.	Deputy Director, Science Operations, Office of the Center Director
Roy Blay, Ph.D.	Office of Scientific Investigations, Reviewer

SPONSOR ATTENDEES:

Robert Dudley Ph.D.	President and CEO
Theo Danoff, M.D., Ph.D.	V.P., Chief Medical Officer

Wael Salameh, M.D.	V.P., Chief Scientific Officer
(b) (4)	Pharmacokinetic Consultant
(b) (4)	Regulatory Consultant
(b) (4)	Regulatory Consultant
Steve Bourne	V.P., Chief Financial Officer
Sandy Faulkner, RN	Clinical Development

BACKGROUND

Clarus Therapeutics, Inc. has designed a new oral self-emulsifying drug delivery system (SEDDS) containing testosterone undecanoate (TU) for potential use as testosterone replacement therapy in hypogonadal men. This formulation consists of TU, the undecanoate ester of testosterone, in a lipid matrix that is intended to favor absorption of TU via the intestinal lymphatics and thus reduce first-pass hepatic clearance. With this formulation, TU is believed to be lymphatically absorbed and subsequently hydrolyzed by endogenous non-specific esterases to release testosterone (T).

Clarus is planning on submitting their NDA in mid to late December, 2013.

DISCUSSION and QUESTIONS

Preliminary responses were provided to the Sponsor on October 4, 2013, in response to the questions posed in the Sponsor's meeting package provided to the Division on September 5, 2013. The Sponsor's questions are presented below in **bolded** text, followed by the Division's responses in normal text. All additional discussion held during the meeting is summarized below in *italics*.

In addition, the Division presented two slides that compared the response of certain safety parameters in oral TU and AndroGel treated subjects. The slides are attached at the end of this document.

CLINICAL

Question 1: Placement of Two Phase 3 Studies in the *e*CTD Structure, Module 5

The submission of the NDA for oral testosterone undecanoate will include two Phase 3 studies, each of which was originally designed to support the proposed indication (CLAR-09007 and CLAR-12011).

As described in Section 6.3, CLAR-12011 will provide the pivotal efficacy data for the application, since this study employed the final proposed dose-titration algorithm. The data from CLAR-09007 will provide supportive data, particularly as it relates to safety.

Clarus originally planned to place both Phase 3 studies in Module 5.3.5.1 "Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication". However, since CLAR-09007 will be included as a supportive study, Clarus requests the Agency's recommendation for the placement of this study in the *e*CTD structure.

What does the Agency recommend for the placement of CLAR-09007 in the eCTD structure of Module 5?

Division Response:
We agree with your original proposal to place both phase 3 studies (CLAR-12011 and CLAR-09007) in Module 5.3.5.1.

In addition, submit all Phase 1 and 2 study reports and results in the relevant subfolders of Module 5.3.3 and include bioanalytical methods in Module 5.3.1.4.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 2: Case Report Forms
Clarus intends to submit Case Report Forms (CRFs) in electronic format only, in accordance with FDA *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (January 2013, rev 3)*. CRFs and subject narratives will be included for only those subjects who died during treatment or within 30 days after last administration of study drug, who experienced an adverse event meeting the definition of serious adverse event, or discontinued from the treatment phase of the study due to an adverse event. Each CRF will be included with the corresponding clinical study report and will be referenced by the report's Study Tagging Files (STF), individually tagged as "case-report-forms". All other case report forms will be available by request.

Does the FDA agree that this is acceptable?

Division Response:
Yes, the planned CRF submission is acceptable. We recommend that you make these narrative summaries and CRFs (of the deaths, serious adverse events and dropouts) linkable from the main body of study reports and the Integrated Summary of Safety.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 3: Integrated Summary of Efficacy (ISE) in Module 5.3.5.3
One study, CLAR-12011, will be included for the assessment of efficacy as this is the only study that incorporates the final proposed dosing algorithm. Clarus anticipates that the text portion of the efficacy analyses will be concise enough to meet the size limitation of Module 2. Therefore, Clarus plans to split the ISE across Module 2 and Module 5 with the narrative portion located in Module 2.7.3, Summary of Clinical Efficacy, and the appendices of tables, figures, and datasets located in Module 5.3.5.3. Reference is made to *Guidance for Industry – Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, (April 2009); Section III.C. ISE-and ISS- Related Differences Between Module 2 and Module 5 of the CTD and eCTD – Exceptions.*

Does the FDA concur with Clarus' approach to the extent and placement of the ISE within the NDA submission?

Division Response:
Yes, we agree with your approach for the ISE submission, with the caveat that both Phase 3 studies (CLAR-12011 and CLAR-09007) assessed efficacy and therefore, both should be discussed in the ISE. If the text required to discuss *both* Phase 3 studies exceeds the Module 2 capacity, then you should provide separate efficacy summaries in Module 2 and in Module 5, respectively.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 4: Integrated Summary of Safety (ISS) in Module 5.3.5.3
Because the number of studies for the assessment of safety is relatively small, Clarus anticipates that the text portion of the integrated safety analyses will be sufficiently detailed to serve as the narrative portion of the ISS, yet concise enough to meet the size limitation of Module 2.

The detailed compilation and interpretation of safety data is also expected to be relatively straightforward. Therefore, Clarus plans to split the ISS across Module 2 and Module 5 with the narrative portion located in Module 2.7.4, Summary of Clinical Safety, and the appendices of tables, figures, and datasets located in Module 5.3.5.3. Reference is made to *Guidance for Industry – Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, (April 2009); Section III.C. ISE-and ISS- Related Differences between Module 2 and Module 5 of the CTD and eCTD – Exceptions.*

Does the FDA concur with Clarus' approach to the extent and placement of the ISS within the NDA submission?

Division Response:
Yes, we agree with your approach for the ISS submission.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 5: Pooled (Integrated) Analysis of Efficacy
The pivotal efficacy data will be based on one Phase 3 study (CLAR-12011). This is the only Phase 3 study which incorporated the final proposed dosing algorithm. Both CLAR-09007 and CLAR-12011 achieved efficacy based on the proportion of subjects with a C_{avg} within the eugonadal range (300-1000 ng/dL). However, the CLAR-09007 results showed a greater number of subjects with a serum testosterone C_{max} higher than desired. To address the number of men with high C_{max} values while maintaining an acceptable proportion with a serum testosterone C_{avg} in the eugonadal range (300-1000 ng/dL), the dosing algorithm used in CLAR-09007 was refined to the final proposed dosing algorithm used in CLAR-12011 (See Table 3).

Efficacy data from the CLAR-12011 clinical study report (CSR) will be provided as the Analysis of Efficacy. Therefore, a "pooled" analysis of efficacy will not be included in the NDA.

Table 3. Summary of Dosing Algorithms for CLAR-09007 and CLAR-12011

Study	CLAR-09007	CLAR-12011
Starting Dose	200 mg BID	200 mg BID
Sampling window for serum T sample used for dose titration decisions	4-6 hours post-dose	3-5 hours post-dose
Down Titration Guidelines • Serum T Concentration • Decrement	• >1100 ng/dL • Titration o Initial - 100 mg BID o Subsequent - 50 mg BID	• >700 ng/dL • 50 mg BID
Up Titration Guidelines • Serum T Concentration • Increment	• <250 ng/dL • Titration o Initial - 100 mg BID o Subsequent - 50 mg BID	• <250 ng/dL • 50 mg BID

Does the Agency concur with the proposed strategy for the analysis of efficacy data?

Division Response:
While it is not necessary, nor appropriate, to "pool" the efficacy data from the two Phase 3 studies, we request that your Integrated Summary (Analysis) of Efficacy include a separate discussion for each Phase 3 study, including analyses and comparisons of the outcomes from the two studies.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 6: Pooled Analysis of Safety
All treated subjects from Clarus sponsored clinical studies of oral TU compiled in the submission will be included in the pooled analysis for safety. The pooled analysis of safety is based on four Phase 2 studies and two Phase 3 studies as compiled in Appendix 1. A total of 540 subjects (377 exposed to oral TU) were enrolled across these studies. The safety analysis set will include all enrolled subjects who received at least one dose of the study drug. All analyses will be presented by treatment group (oral TU and transdermal T-gel).

The primary focus of the pooled analysis of safety will be on the clinical safety of oral TU. Key analyses for safety will consist of the following:

- **Number and incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, treatment-related TEAEs, serious treatment-related TEAEs, TEAEs leading to permanent discontinuation of study medication, and TEAEs leading to death.**
- **Laboratory assessments with a focus on endpoints known to be affected by T replacement, including hematocrit (HCT), lipids [high density lipoproteins (HDL) and low density lipoproteins (LDL)] and prostate specific antigen (PSA).**
- **Vital signs and medical history listings.**
- **Concomitant medications summarized by pooled TU and T-gel treatment and by therapeutic class and preferred term.**
- **Summary of study population data: Demographic and baseline characteristics will be summarized using descriptive characteristics appropriate for continuous variables such as age, height, weight, and BMI.**
- **Extent of exposure analysis presented by both pooled overall oral TU and T-gel treatment groups.**

Does the Agency concur with the described approach for the pooling of the safety data?

Division Response:
Yes, we agree with your approach for the safety analysis. We note, however, that none of the appendices in your meeting package contained a compilation of patient exposure or patient safety data, as referenced in your Question 6. In addition, we point out that in light of the clinical safety observations described below, the sufficiency of the overall size of the clinical trial safety database (377 patients exposed to TU) will be a review issue.

In addition to the clinical trial safety data collected for your product, we request that your NDA submission contain a summary of postmarketing experience with TU products that have been marketed outside the U.S.

Further, we have the following preliminary Clinical comments and requests in regard to the Summaries of Phase 3 and dihydrotestosterone (DHT) data that you provided on September 23 and September 30, 2013 in response to our Information Requests:

1. Results from CLAR-09007 showed higher DHT concentrations, higher PSA, greater HCT, lower HDL, and worse cardiovascular (CV) biomarkers in the TU treated group compared to the AndroGel treated group. Address the potential clinical significance of these safety observations in your NDA submission.

2. Provide the following items in your NDA submission to address potential safety concerns with your product:
    a. An integrated analysis of DHT exposure and DHT/T ratio associated with your product relative to eugonadal range and active comparator DHT exposures and DHT/T ratios.
    b. An exposure-response analysis of DHT and T concentrations associated with your product relative to observed changes in HCT, PSA, HDL, and CV biomarkers.

c. A discussion of potential long-term safety risks, if any, associated with the DHT exposures and DHT/T ratios observed with your product.

Additional Discussion:
The Sponsor requested clarification of the Division's request for a summary of post-marketing experience with TU products available outside the U.S. The Sponsor stated that it has access only to data available in the public domain (e.g., published literature) and asked whether that would be sufficient. The Division stated that data available in the public domain would be sufficient. The Sponsor also asked whether the request applied to oral TU products only. The Division stated that the request applied to oral TU products only.

The Division referred to two FDA-prepared slides that compared the response of certain safety parameters in oral TU and AndroGel treated subjects. One slide was a summary of the cardiovascular (CV) biomarker non-inferiority analysis (as provided by the Sponsor) and the other was a summary of changes from baseline to Day 365 for hematocrit, PSA and HDL cholesterol (HDLc). The Sponsor sought clarification of the FDA statement "…worse cardiovascular (CV) biomarkers in the TU treated group compared to the AndroGel treated group." The Division responded that the Sponsor had pre-defined the parameters for "worsening" of CV biomarkers, and in this regard, there appeared to be more worsening from baseline for oral TU as compared to AndroGel.

The Sponsor stated that oral TU was found to be non-inferior to AndroGel by the Sponsor's statistical analysis. The Sponsor's interpretation of the data is that TU was not 'worse' than AndroGel. The Sponsor acknowledged numerical differences between groups but pointed out that these differences were numerically small and not clinically meaningful. The Division pointed out that the difference between groups, at least for CV biomarkers, was statistically significant. The Division further stated that the original protocol synopsis called for a 10% non-inferiority margin, not a 20% margin, and the upper bound of the 95% CI exceeded 10% for the CV biomarkers.

There was additional discussion of these results, including discussion of 1) the reduction in dose of oral TU subsequent to Study CLAR-09007, 2) the relationship between worsening of CV biomarkers and T exposure, 3) the sensitivity of HDL cholesterol (HDLc) as a biomarker of CV risk, 4) the analysis of additional, potentially more sensitive biomarkers of CV risk (e.g., cholesterol efflux and HDL particle number), 5) the analysis of other potentially clinically relevant biomarkers (e.g., body composition parameters), and the 6) the clinical relevance of the non-inferiority margin, including the issue of normal variability in the assayed biomarkers (e.g., hs-CRP).

The Division stated that the Sponsor should provide a detailed discussion in the NDA of these issues, complete with data and analyses, to address the concerns reflected in the two FDA-prepared slides.

The Sponsor inquired about the Division's opinion of which is more clinically important – DHT concentration or DHT/T concentration ratio? The Division stated both DHT concentration and DHT/T ratio are currently considered clinically important. The Sponsor will address DHT exposure in relation to key safety parameters in the NDA.

The Division responded that the Pharmacometrics group will also review these data thoroughly. Pharmacometrics stated it would be useful to combine both trials and analyze the exposure-safety biomarker relationship to see whether the two trials have a consistent relationship and to determine whether the T exposure difference between the two trials can explain the difference in CV biomarker levels. The Sponsor acknowledged these recommendations.

Question 7: Follow-up Safety Data

Subjects who completed 12 months of treatment in CLAR-09007 were eligible for enrollment into the long-term safety follow-up study (CLAR-12010) for up to an additional 12 months. No new subjects were recruited into CLAR-12010. Subjects who completed CLAR-09007 and were willing to participate in CLAR-12010 were rolled over and continued on the treatment to which they were randomized in CLAR-09007. A description of this study is as follows:

CLAR-12010 – "Phase IV, Open-label study of Oral Testosterone Undecanoate in Hypogonadal Men"

This is a one year extension study for hypogonadal men treated with oral TU or AndroGel who completed the 12-month Phase III study CLAR-09007. No new subjects were recruited into this study; all subjects in this study were rolled over from CLAR-09007 and continued on the treatment that they were randomized to in CLAR-09007. The primary objective of this one year extension study is to gather additional safety data. This study will allow safety data from exposure of up to 24 months of dosing based on 12 months of dosing in CLAR-09007 and up to 12 months in CLAR-12010. Safety will be assessed on the basis of physical exam, clinical chemistry and hematology, cardiovascular biomarkers (specifically, Lp-PLA2 and hs-CRP), prostate volume, and adverse event reporting.

There are five visits planned during which safety evaluations will be performed (see Table 4 in the briefing package for details). The Day 365 visit of CLAR-09007 served as the Day 0 visit (Visit 1) of CLAR-12010. Safety assessments are made at four subsequent visits which occur every ≈90 days, with the last visit, Visit 4, occurring at Day 365. Dose adjustment was allowed on 2 occasions based on a 4-6 hour post-dose serum testosterone concentration sample drawn at Visit 1 (Day 0) and Visit 3 (Day 180).

Eligible subjects who completed CLAR-09007 rolled over into CLAR-12010, (88 subjects on TU oral and 94 subjects on T gel). The last patient enrolled in CLAR-12010 in April 2013. Available safety data from CLAR-12010 will be included in the 120-Day Safety Report.

Based on an anticipated NDA submission date of December 2013, the 120-Day Safety Report will be submitted April 2014. With an approximate February 2014 data cut-off date for the Day 120 Safety Update, data will be available for essentially all subjects who have completed Day 180 and Day 270 visits. In addition, approximately 50% of available subjects will have Day 365 data. Although there is ongoing data review, the data for the 120 Day update will not be fully monitored and verified. Data will be supplied as a brief report with Tables and Listings and will not be integrated with the ISS data since it does not include any new subjects and is intended to report extended exposure of subjects included in the ISS (subjects reported in the CLAR-09007 study).

Review of this data will allow an evaluation of the safety profile for subjects exposed for more than 365 days on TU oral or T gel.

Notably, Serious Adverse Events (SAEs) reported up to the time of the 120-Day Safety Update will be included and will not be limited to the February data cutoff.

Clarus would appreciate the opportunity to consult with the Agency regarding further details on the format and content of the 120-Day Safety Report.

Does the Agency concur with the proposed approach for reporting the long-term safety data?

Division Response:
Yes, we agree with your approach to submit the preliminary data from Study CLAR-12010 with the 120-day Safety Update. In addition to Tables and Listings, we request that the submission include datasets.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 8: Sites for Inspection
In order to assist the clinical reviewer in selecting sites for inspection, Clarus plans to include a table in the NDA which will include the following information for the pivotal Phase 3 clinical trial, CLAR-12011:

1. **Site number**
2. **Principal investigator**
3. **Location: City, State (all sites are within the US)**
4. **Number of subjects screened**
5. **Number of subjects randomized**
6. **Number of subjects treated who prematurely discontinued (or other characteristics of interest that might be helpful in choosing sites)**
7. **Number of significant protocol deviations**

The table will be located in Module 5.3.5.1.

Does the FDA concur with format, content, and location within the eCTD structure of the site inspection information?

Division Response:
No. You should review the information provided by the Office of Scientific Investigations (OSI) in the section titled "*INSPECTION INFORMATION*" located at the end of this document. Indicate how you will be responding to each requested item in Parts I, II, and III of this section.

In addition to the Clinical sites, provide pertinent information for all bioanalytical sites. If there are multiple bioanalytical sites, include a summary listing of all patients for each site.

Additional Discussion:
The Sponsor requested clarification as to whether the Division would like a summary listing for the subjects on the TU product only. The Division responded that they had conferred with the OSI Division of Bioequivalence & Good Laboratory Practice Compliance and was informed that the listing should include subjects in the TU treatment group and in the comparator arm (i.e. AndroGel.

The Division further reminded the Sponsor to provide the information for Study CLAR-12011 as well as for Study CLAR-09007.

The Division inquired about the number of bioanalytical sites used for Phase 3 studies CLAR-12011 and CLAR-09007. The Sponsor stated that just one bioanalytical site (b) (4) *was used for both studies.*

NONCLINICAL

Question 9:Waiver from Conducting Reproductive and Developmental Toxicology Studies
In accordance with the FDA Guidance for Industry – M3 (R2), "*Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010, Rev 1)", r*eproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed.

Developmental toxicity studies are not considered necessary since the sole target population consists of men. Also, because of the intended use of the compound, there would not be a medical need for treatment of women of child-bearing potential. Moreover, exposure of a pregnant woman to exogenous testosterone may result in fetal harm - - an already well-established effect.

Testosterone replacement in men with secondary hypogonadism may result in reduced sperm count due to the negative feedback inhibition of LH and FSH. This pharmacological action of exogenous testosterone is well established in the published medical literature.

Sufficient data are available in the public domain relative to the developmental and reproductive toxicity profile of oral TU specifically and of testosterone generally to obviate the need of further studies. New studies of oral TU will not provide any further insight and will result in the unnecessary use/death of laboratory animals.

***Reproductive Toxicity*:**

As reported in publicly available documents, a study was conducted in which sexually mature male rats were given 5, 20 or 80 mg/kg/day of testosterone undecanoate or placebo orally for 9 weeks prior to and for 2 weeks during mating with untreated females. First generation (F0) males were subjected to further matings 3, 10 and 14 weeks after cessation of treatment. Half of the females were examined after 20 days of gestation while the remainder continued to term and reared their young to 28 days of age. Second generation (F1) males and females were selected and mating performance and fertility evaluated.

At a dose of 80 mg/kg/day, impaired fertility occurred and increased pre-implantation loss (reduced litter size) was observed in females mated with treated male rats. This effect appeared to be reversible. With the exception of a reduced post-weaning body weight of male progeny derived from the final mating, growth, development and fertility of offspring were similar in all groups. Autopsy of F0 males 18 weeks after cessation of 80 mg/kg/day revealed a significant reduction in both absolute and relative testes weight.

Does the Agency agree that nonclinical studies of fertility in male and female animals and of reproductive and developmental toxicity in female animals are not necessary for marketing application of testosterone undecanoate and that submission of a Waiver will not be required?

Division Response:
No. We do not agree. Nonclinical information is necessary for approval of a marketing application for testosterone undecanoate. However, if you intend to pursue a 505(b)(2) regulatory pathway, you may meet this requirement by relying upon appropriate published literature and establishing that reliance on the studies described in the literature is scientifically appropriate. You should also include a copy of the published literature in the application and identify any listed drugs described in the published literature.
Please see additional information in the section titled "*505(b)(2) REGULATORY PATHWAY*" located at the end of this document.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

BIOSTATISTICAL

Question 10: Statistical and Electronic Datasets
Clarus intends to submit the New Drug Application (NDA) in electronic Common Technical Document (*e*CTD) format with the following XML definition files.

***e*CTD Supportive Files**	**Version**
ICH *e*CTD DTD	3.2
ICH-STF DTD	2.2
US Regional DTD	2.01

Clarus intends to include Case Report Tabulation (CRT) as part of the NDA submission. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM 1.2 IG 3.1.2) for all Phase 2 and 3 clinical studies (Appendix 1). In addition, the Sponsor plans to submit Analysis Data published in scientific data set (SDS 1.6 – ADaM IG 1.0) format along with Source Data published in SDS 1.6 (ADaM IG 1.0, SAS .XPT) format for the Phase 3 studies only.

Does the Agency agree with the proposed outline regarding the scope, format, and documentation of the electronic datasets to be submitted?

Division Response:
We agree with the proposal.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 11: Dissolution Method
Clarus is providing information in the meeting package as follow-up to the FDA's preliminary responses (dated 20 August 2012) to a question posed by Clarus in the End of Phase 2 (EOP2) Type B CMC Meeting Request (IND 78,104, Serial No. 0042). Clarus requested feedback on the current dissolution method to evaluate *in vitro* release of testosterone undecanoate. Clarus also asked for feedback on the dissolution data provided in the briefing document to support development of the dissolution method. The dissolution method is included in the drug product specification as a release and stability test.
As recommended by FDA in its response to Clarus' EOP2 CMC package/questions, Clarus has collected additional data regarding the current dissolution method, including:

- **Assessment at 50, 75 and 100 RPM paddle rotation speeds (Apparatus 2) with generation of dissolution profiles from 10 to 60 minutes;**
- **Assessment at three levels of Triton X-100 surfactant in the dissolution medium; and**
- **Assessment of an alternate surfactant and buffer.**
- **Initial dissolution studies conducted with three batches of testosterone undecanoate (TU) soft gelatin capsules** (b) (4) **The 75 RPM paddle speed was selected for the dissolution method. Using a 75 RPM paddle speed, three concentrations of Triton X-100 surfactant in the dissolution medium** (b) (4)**, 1.0%** (b) (4) **were evaluated. From these studies, it was determined that a concentration of 1.0% Triton X-100 in the dissolution medium provided adequate sink conditions and enabled statistical discrimination between the three batches of capsules. Further studies showed that** (b) (4) **for analysis of TU capsules. In addition,** (b) (4) **did not offer any advantage over the current pH 6.8 phosphate buffer as in the dissolution medium. The dissolution method development studies led to the selection of a 75 RPM paddle speed and 1.0% Triton X-100 in pH 6.8 phosphate buffer as the dissolution medium for dissolution testing of TU**

capsules. The new dissolution method conditions are being used to test drug product on stability studies in a cross-over manner.

- **Subsequent dissolution testing using an additional four batches of TU capsules, 100 mg and 150 mg, confirmed the selection of the above new dissolution method conditions. The additional data support a dissolution specification of Q= (b) (4)% at (b) (4) minutes for TU capsules. Because all capsules evaluated in the dissolution studies were within the drug product specifications (i.e., assay NLT (b) (4)% TU and total degradation products NMT (b) (4)%), a dissolution specification of Q= (b) (4)% at (b) (4) minutes is considered reasonable to avoid unnecessary failure of batches (and unnecessary re-testing) when USP Acceptance Criteria are applied to the dissolution data for aged capsules.**
- **The proposed new dissolution method was validated. The method met the established acceptance criteria for specificity, linearity, recovery, precision, filter performance, robustness, and solution stability.**
- **The capsules used in the dissolution studies were all manufactured at the intended commercial scale according to the proposed commercial formulation using the intended commercial process and production equipment. All batches were manufactured by (b) (4) -- the intended commercial production site. The batches were all used in clinical trials and/or for NDA registration stability purposes. All of the batches have been entered into long-term ICH stability studies.**
- **The dissolution studies were conducted by (b) (4) facility and (b) (4) capsule units were used for most of the dissolution experiments. The dissolution data were analyzed using Analysis of Variance and USP Acceptance Criteria, where appropriate. The dissolution method development and validation studies were performed in several stages (referred to as Stages A, B1, B2, C, D, E and F). A Dissolution Summary Report and detailed report for each stage of the dissolution studies are included in Section 10, Appendices 1-8.**

Does the Agency agree that the additional dissolution method development studies performed are sufficient to support Clarus' conclusions about paddle rotation speed and surfactant selection for the dissolution method and the time point and proposed Q value for the dissolution specification?

Division Response:
The additional dissolution method development studies support your paddle speed selection for the dissolution method. However, we request that you justify selection of Triton X-100 as your surfactant of choice instead of other commonly used non-ionic surfactants, such as Tween (polysorbates), Cremophor (polyoxyl castor oil), and polyoxyl lauryl esters. Based on the dissolution data provided for your drug product at your proposed dissolution method, we recommend you accept the dissolution acceptance criterion of Q = (b) (4)% at 30 minutes;

however, the final recommendation regarding the acceptability of the acceptance criterion will be based on overall dissolution data from the bio-batches (both pharmacokinetic and clinical) and registration batches under the NDA. In addition, we suggest that you not use the (b) (4) minute time point in the overall dissolution profile data due to the high variability observed at (b) (4) minutes.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 12: Drug Substance
Clarus will submit two drug substance manufacturers in the NDA: (b) (4) and (b) (4), a wholly owned subsidiary of (b) (4) Clarus proposes to provide a separate Module 3.2.S for (b) (4) and for (b) (4). The format and structure of each manufacturer's Module 3.2.S will be consistent with FDA *Guidance for Industry, M4Q: The CTD – Quality, August 2001*. Clarus will provide a single integrated Quality Overall Summary with respect to drug substance in Module 2.3.S.

Based on the information provided in the pre-meeting Information Package, does the Agency agree that the organization of the CMC information for Drug Substance in the NDA is adequate?

Division Response:
We agree that the organization of the drug substance information is adequate.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

REGULATORY

Question 13: Pediatric Waiver
Clarus plans to include a Waiver from Conducting Pediatric Studies (Module 1.9.1) in the NDA submission to fulfill the requirement for a pediatric assessment under the Pediatric Research Equity Act (PREA).

The request will include a full waiver for studies in all pediatric age groups for the reason that necessary studies are impossible or highly impractical because the number of subjects in this population is so small.

Can the Agency confirm that this is acceptable?

Division Response:
Your request for a full pediatric waiver will need to be reviewed by the Pediatric Review Committee for their advice and recommendation.

Regarding timing of your request, according 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. , if you submit an NDA that triggers PREA before January 5, 2014, the FDA intends to exercise enforcement discretion with regard to the new provisions found in FDASIA that require an agreed-upon initial Pediatric Study Plan (PSP) be submitted as part of the application. However, the FDA encourages sponsors who are planning to submit such an application before January 5, 2014, to submit an initial PSP for review as soon as possible. Sponsors should be aware that review of and agreement to an initial PSP generally will require at least 7 months. If an agreed-upon initial PSP is not included in the application, the sponsor should submit a description of the planned or ongoing studies as previously required under PREA.

For additional information please see the section titled "*PREA REQUIREMENTS*", located at the end of this document.

Additional Discussion:
The Sponsor stated that they plan to submit the NDA in December 2013. For an NDA that would be submitted prior to January 5, 2014, the Division encouraged the Sponsor to submit the PSP in advance of submitting their NDA. If the NDA submission would follow shortly after a PSP, it is acceptable to instead submit a pediatric waiver request with justification in the NDA. The Division confirmed that if the Sponsor submits a PSP in advance of their NDA submission, then they should also include the PSP in the NDA.

Post-Meeting Comment: As noted in the draft Guidance for Industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf), if you submit your NDA on or after January 5, 2014, you must include an agreed-upon PSP with the application (i.e., a PSP that has already been submitted, reviewed, and agreed-upon by the Division in consultation with the Pediatric Review Committee).

Question 14: Environmental Analysis
In accordance with the FDA *Guidance for Industry*, *"Environmental Assessment of Human Drug and Biologics Applications", July 1998, Rev 1* and 21 CFR 25.31, Clarus is requesting categorical exclusion from the environmental assessment requirement for the product testosterone undecanoate.
The Clarus formulation of testosterone undecanoate qualifies for a categorical exclusion because:

- **The calculated EIC-Aquatic for testosterone is less than 1ppb (1µg/L).**
- **It will not result in additional incidental exposure to testosterone in the human environment. In fact, it may decrease the opportunity for incidental or unintended exposure of sensitive populations (e.g., women and children) to testosterone.**
- **The active ingredient is naturally found in the environment, and this formulation will not result in a biologically significant increased amount in the environment.**

- **There are no known extraordinary circumstances, as defined by the FDA Guidance (FDA, 1998).**

The request for categorical exclusion is based on a report entitled, "Environmental Impact for Testosterone Undecanoate: Request for Categorical Exclusion" dated August 19, 2013 and prepared by Christopher Chengelis, Ph.D., D.A.B.T. A copy of this report is included (Appendix 9) and will be submitted in Module 1.12.14 Environmental Analysis, in the NDA.

Does the FDA concur that an Environmental Assessment would not be required?

Division Response:
We cannot concur at this point that an environmental assessment (EA) would not be required. While your estimated introductory concentration (EIC-aquatic) is less than the 1 µg/L categorical exclusion level, published literature indicates that this product has the potential for harm to the environment at the expected level of exposure. Thus, this product might constitute an "extraordinary circumstance" under 21 CFR 25.21. Also, while we agree that the orally delivered formulation might decrease incidental or unintended human exposure, this cannot necessarily be said of exposure to aquatic organisms, given the apparent increase in total use of the active moiety noted in your August 19, 2013 estimate. Additional information will be required to demonstrate that this product will displace currently marketed testosterone products without significantly increasing environmental introductions of testosterone or metabolites. As described in Section II of the EA guidance and in the preamble to 62 FR 40570 (July 29, 1997), information such as this, including the ratio of the predicted environmental concentration to the predicted no-effects concentrations (PEC/PNEC), aid in determining whether extraordinary circumstances exist and thus whether the criteria for a categorical exclusion have been met.

Additional Discussion:
The Sponsor stated that they are not aware of data to show potential for harm to the environment at the expected level of exposure. The Division expressed concern in regard to the Sponsor's projection of a large anticipated market use. The Sponsor's projections (estimated at (b) (4) *kilograms per year as compared to the existing level of* (b) (4) *kilograms per year for currently approved products) led the Division to believe that the use would be* (b) (4) *the use of currently approved topical products.*

The Sponsor stated that this is an accurate projection but wanted to point out that with a topical product, approximately 80% remains on the skin and is not absorbed into the body. Therefore, much of the product gets washed off in the shower. Since the Clarus product will be taken orally, that will not be the case.

The Division requested that the Sponsor submit literature to support their reasoning as to why a categorical exclusion should be granted for their product.

The Division offered examples of the following literature that is available to support the potential for harm:

1. *USEPA (2012). Revisions to the Unregulated Contaminant Monitoring Regulation (UCMR 3) for Public Water Systems, 77 Federal Register 26071. The US Environmental*

Protection Agency (EPA) recently finalized this rule under the Safe Drinking Water Act (SDWA) requiring public water systems to monitor testosterone and six other hormones as part of the UCM Program.

2. *Bellet, V., G. Hernandez-Raquet, et al. (2012). "Occurrence of androgens in sewage treatment plants influents is associated with antagonist activities on other steroid receptors." Water Research 46(6): 1912-1922.*

3. *Hoffmann, F. and W. Kloas (2012). "Effects of environmentally relevant concentrations of the xeno-androgen, methyldihydrotestosterone, on male and female mating behavior in Xenopus laevis." Chemosphere 87(11): 1246-1253. This reference highlights the cumulative risk that additional testosterone contributes to total androgenicity.*

4. *Deksissa, T. (2008). Fate and Transport of Steroid Hormones in the Environment. Abstracts of presentations given in session 8 of the 2008 UCOWR Conference, Southern Illinois University Carbondale, Water Resource Research Institute and Agriculture Experiment Station, University of the District of Columbia.*

5. *Leon, A., S. J. Teh, et al. (2007). "Androgen disruption of early development in Qurt strain medaka (Oryzias latipes)." Aquatic Toxicology 82(3): 195-203.*

6. *Thomas, K. V., M. R. Hurst, et al. (2002). "An assessment of in vitro androgenic activity and the identification of environmental androgens in United Kingdom estuaries." Environmental Toxicology and Chemistry 21(7): 1456-1461.*

7. *Khan, U. and J. Nicell (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. This ref. presents a ratio of the predicted environmental concentration to the predicted no-effects concentrations (PEC/PNEC).*

Question 15: Labeling

The proposed package insert will be provided in accordance with the physician's labeling rule (PLR), 21 CFR 201.56-57 and the FDA *Guidance for Industry, Labeling of Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, February 2013*.

Clarus plans to submit labeling consistent with the other testosterone products excluding the black box warning that applies to transference risk of testosterone topical gel/solution products. Clarus does not envision the need for a similar warning related to transdermal transfer since testosterone undecanoate is an oral formulation.

Does the Agency concur?

Division Response:
Yes. We agree that the boxed warning for testosterone transdermal products is not applicable to your product.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 16: Risk Management Plan
In accordance with the Food and Drug Administration Safety and Innovation Act (FDASIA, Section 905), and PDUFA V, the FDA will implement a structured risk-benefit assessment framework during the NDA approval process.

Clarus does not plan to include a Risk Management Plan (Module 1.16) in the NDA submission. After FDA review of the safety information included in the NDA, Clarus will be agreeable to further recommendations from the Agency for a post-approval risk management program.

Is the FDA agreeable to this approach?

Division Response:
Yes. We agree with your approach.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 17: Proprietary Name
Clarus submitted a Request for Proprietary Name to IND 78,014 [SN0056] on 2 January 2013 (b) (4) On 6 March 2013, the Division of Medication Error Prevention and Analysis (DMEPA) responded that the proprietary name request was unacceptable (b) (4)

(b) (4)

Clarus contacted DMEPA on 20 June 2013 to determine when action on its appeal could be expected. DMEPA responded that a definitive response date could not be provided but Clarus' request for reconsideration (b) (4) was under active review. Clarus contacted DMEPA again on 12 August 2013 for a status report. DMEPA responded that they are working expeditiously to complete the review.

FDA review period for Proprietary Name Requests is shorter for requests submitted during the NDA review phase than for requests submitted to the IND. Therefore,

depending on when Clarus is notified by DMEPA of it decision (b) (4) Clarus may continue communication under the IND or withdraw the request from the IND and re-submit to the NDA after the application has been dispatched.

Does the FDA concur with Clarus' strategy?

Division Response:
We do not recommend that you withdraw your Proprietary Name Request from your IND submission. You will receive an action letter regarding your request for reconsideration from DMEPA no later than October 16, 2013.

Irrespective of the outcome of that action, you will need to resubmit a Proprietary Name Request with your NDA submission. All Proprietary Name Requests are considered conditional/tentative until the product receives an approval action.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

ADDITIONAL QUESTIONS
Question 18:
Does the Agency anticipate requesting an Applicant Orientation Meeting for the NDA?

Division Response:
No. We do not currently anticipate the need for an Applicant Orientation meeting.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 19:
Does the Agency anticipate that the NDA will be subject to a DBRUP/FDA Advisory Committee meeting?

Division Response:
We cannot determine if an Advisory Committee (AC) meeting is needed for this application until your NDA is submitted. However, we cannot rule out this possibility. If during our filing review the Division decides that an AC meeting would be of benefit, you will be notified in the 74 day letter. It is also possible that an AC could be determined at a date after the 74 day letter if we subsequently uncover issues during our review requiring external expertise.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

Question 20:
Does the Agency agree with the overall scope, format and content of the proposed NDA?

Division Response:
The overall scope, format and content of the proposed NDA appear reasonable. We have the following additional Clinical and Clinical Pharmacology comments and requests:

1. Submit a summary of postmarketing experience with TU products that have been marketed outside the U.S.

2. Clarify whether the to-be-marketed formulation of TU capsules was used in the two Phase 3 studies.

3. Preliminary results from Study 09008 showed that testosterone bioavailability is increased with increasing fat content of meals. You propose that TU capsules be taken with food (not on an empty stomach or with a very low fat meal). In your NDA submission, discuss your proposed dosing instructions as it relates to food intake by patients in the Phase 3 Study CLAR-12011 and in the food effect Study 09008.

4. Submit all datasets and codes used for modeling and simulation.

   We encourage you to refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm):

   a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). Codes and output listings for trial simulation used to evaluate the impact of each factor should be submitted.
   c. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results."

Additional Discussion:
In regard to Item #3, the Division noted that there appears to be a difference between the Phase 3 study design and the proposed dosing instructions with respect to food administration. The protocol for the Phase 3 study CLAR-12011 states only that patients should take TU with meals, not on an empty stomach. The proposed dosing instructions in the pre-NDA meeting package is to take TU with the morning and evening meal, not on an empty stomach or with a very low-fat

meal. The Division reminded the Sponsor that the dosing instructions for an approved label will reflect the dosing instructions in the Phase 3 study.

Question 21:
Has the Agency identified any issues that would pose a barrier to the fileability of this NDA?

Division Response:
A decision regarding fileability will be made after the Division's preliminary review of the submitted application.

Additional Discussion:
The Sponsor stated that no additional discussion was necessary.

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.

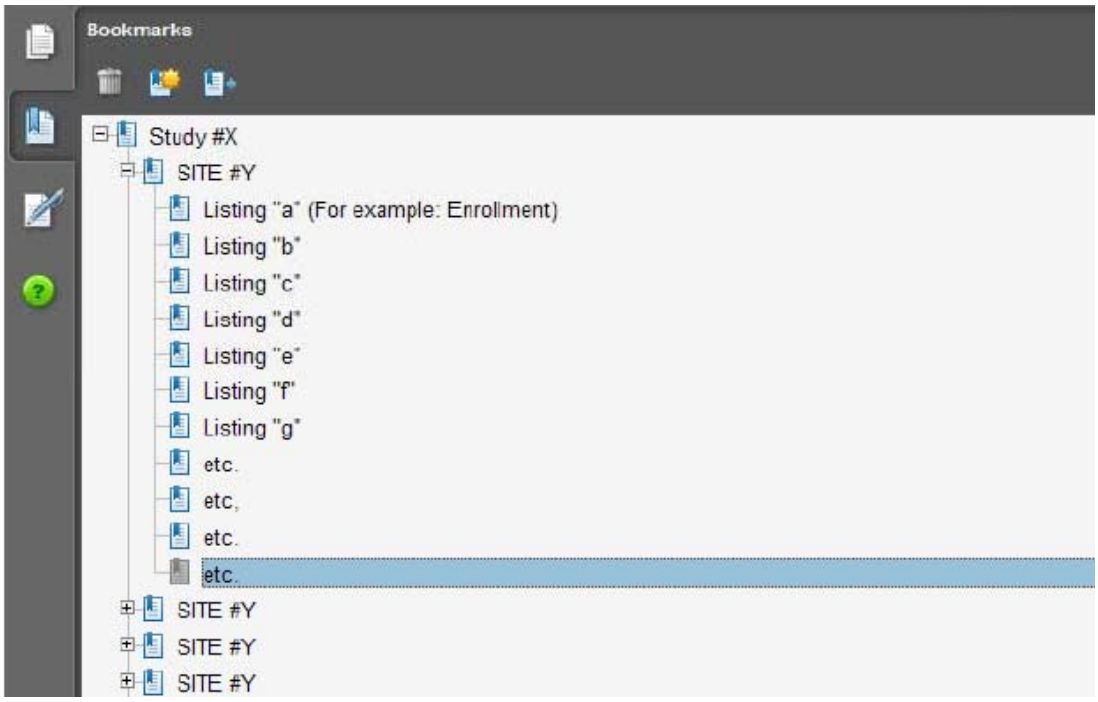
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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[1]	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.

[1] 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

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
See attached

Main safety concerns: HCT, PSA and HDL (Change from baseline in two Phase 3 trials)

Clinical Labs	**CLAR-09007** (Change at Day 365)		**CLAR-12011** (Change at Day 114)
	Oral TU	**T-Gel**	**Oral TU**
HCT (%)	2.9% (±3.9)	1.4% (±3.3)	3.3% (±3.1)
PSA (ng/ml)	0.27 ±0.72	0.19 ±0.5	0.3 ±1.2
HDL (%)	-22% (±14)	-12% (±13)	-9.9% (±18)

CV biomarkers (hsCRP and Lp-PLA2) in CLAR-09007:

Pre-specified "Worse": >50% increase for either biomarker at Day 365; Pre-specified NI margin: <20% difference in the "Worse" (UB of 95%CI)

Crude Counts for Risk Classification	Oral TU (N=161) n (%)	T-gel (N=160) n (%)	Total Both Groups	P-Value[1]
Worse	27 (21.6)	22 (16.7)	49	
Not Worse	98 (78.4)	110 (83.3)	208	
Proportion Worsening Point Estimate (95% CIs)	0.216 (0.147, 0.298)	0.216 (0.147, 0.298)		0.3432
Difference between Oral TU and T-gel in the proportion worsening point estimate (Oral TU – T-gel; 95% CI)	0.049 (-0.074, 0.171)			

1- P-value is from Fisher Exact Test.

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

/s/

MARK S HIRSCH
11/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078104

MEETING MINUTES

Clarus Therapuetics, Inc
Attention: Robert E. Dudley, Ph.D.
President and CEO
500 Skokie Blvd., Suite 250
Northbrook, IL 60062

Dear Dr. Dudley:

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

We also refer to the meeting between representatives of your firm and the FDA on February 1, 2010. The purpose of the meeting was to discuss a summary of your phase II data and synopses of protocols in your phase III development plan.

A copy of the official minutes of the meeting is attached 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}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproduction and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**Type C**
Meeting Category:	**Guidance**
Meeting Date and Time:	**February 1, 2010@1:30-3:00 p.m.**
Meeting Location:	**White Oak Building #22, Conference Room 1417**
Application Number:	**IND 078104**
Product Name:	**Oral testosterone undecanoate**
Indication:	**Testosterone replacement therapy**
Sponsor/Applicant Name:	**Clarus Therapeutics, Inc.**
Meeting Chair:	**Mark Hirsch, M.D.**
Meeting Recorder:	**Jeannie Roule**

FDA ATTENDEES:

Scott Monroe, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D.	Medical Team Leader, DRUP
Harry Handelsman, M.D.	Medical Officer, DRUP
Jeffrey Bray, Ph.D.	Pharmacology/Toxicology Reviewer, DRUP
Myong-Jin Kim, Pharm. D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology (DCP) III, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Doanh Tran, Ph.D.	Clinical Pharmacology Reviewer, DCP III, OCP, OTS
Mahbob Sobhan, Ph.D.	Team Leader, Division of Biometrics III, Office of Biostatistics, OTS
Jennifer Mercier	Chief, Project Management Staff, DRUP
Jeannie Roule	Regulatory Health Project Manager, DRUP

EXTERNAL CONSTITUENT ATTENDEES:

Robert Dudley, Ph.D.	President & CEO
(b) (4) (b) (4)	Principal Investigator and Medical Consultant. (b) (4) Pharmacokinetic Consultant
Sandy Faulkner, R.N.	Director of Clinical Research
(b) (4)	Statistical consultant

BACKGROUND

Clarus Therapeutics has been developing an oral formulation of testosterone undecanoate for testosterone replacement therapy in hypogonadal men. The formulation employs a self-emulsifying drug delivery system (SEDDS) to promote lymphatic absorption of testosterone in the intestinal tract.

DISCUSSION

The following preliminary draft responses were provided to the Sponsor on January 29, 2010, in response to the questions posed in the sponsor's meeting package. The sponsor's questions are presented below in **bolded** text, followed by the Division's responses in normal text. All additional meeting discussion and post meeting comments are summarized in *italics.*

Question #1

In view of the fact that Clarus has now answered questions raised by DRUP regarding time to steady-state, identification of an optimal single sampling time point for blood collection on which to base dose titration, and food effect, we believe additional Phase II studies are not needed to support Phase III testing of Clarus's oral TU product.

Does DRUP agree?

Response: We agree that no further Phase 2 studies are needed to support Phase 3 testing; however, additional discussion is required before we can agree to the design of your Phase 3 clinical trials. We remain concerned by:

1. Elevated serum DHT concentrations and supraphysiologic DHT/T ratios observed in Phase 2 development. These findings will necessitate a long-term safety study to assess their clinical significance. The type of study, its duration, endpoints, and number of subjects are still under consideration (see our response to Question #2).

Additional Discussion: The Sponsor stated their belief that the proposed 12-month, Phase 3, open-label study and 12-month postmarketing extension is sufficient for safety. The Division reiterated its concern relevant to high DHT concentrations and high DHT:T ratios observed with the Clarus product, despite Clarus' contentions that serum DHT was no higher with their product than with currently approved T replacement products. The Division noted that a small, head-to-head, multiple-dose, PK study comparing the Clarus product to a standard approved T replacement product (e.g., AndroGel) might be useful to support the Sponsor's contentions prior to Phase 3, but such a study is not a requirement. The Division clarified that the safety concern for high DHT was more relevant to previously observed increases in hemoglobin and hematocrit and adverse effects on serum lipids (as markers for risk of stroke and cardiovascular disease), rather than prostate effects. The Sponsor expressed the belief that all androgens can affect hemoglobin, hematocrit, and serum lipids. The Division maintained that a long-term (e.g., 2 year), active-controlled trial could determine whether the Clarus product was worse than existing testosterone replacement therapies in this regard. The Sponsor agreed to consider conducting an active-controlled, Phase 3 study. The Division encouraged the Sponsor to submit a proposal for cardiovascular markers to be assessed in the Phase 3 trial. The Sponsor inquired as to the number of subjects for the Phase 3 study. The Sponsor proposed studying 180 subjects with the objective of completing 150. The Division had considered a larger number of subjects, but would be guided by sample size calculations for key safety parameters and comparisons between treatment groups.

2. Variability in T levels related to fat content in the patient's diet. The clinical significance of these findings is still unclear.
    a. Food effect study CLAR-09008 indicates that there were significant differences in bioavailability of testosterone (T) following administration with very low fat to high

fat meals. Therefore, if a patient does not have a consistent diet, his testosterone exposure is expected to fluctuate depending on the fat content of a particular meal. In an extreme case, a patient who had consistently consumed a very low fat diet and was titrated to a T Cavg of 900 ng/dL, could exhibit a higher T Cavg of perhaps 1350 ng/dL if he were to change to a high fat diet. This issue needs further discussion.

- One potential path forward is to reduce the target range for T Cavg and Cmax so that even in the event of potential fluctuations in absorption due to the type of food intake, a patient with Cavg in this narrower range would still meet the normal efficacy and safety requirements for a testosterone drug product. Modeling and simulation may be used to support a proposed new target range.

b. We recommend that no restriction be placed on the type of meals consumed during the Phase 3 study, including pre-dose meals on pharmacokinetic sampling days.

Additional Discussion: The Sponsor stated that there was a modest, not clinically significant increase in absorption of the product with high fat meals compared to low fat meals, except in the case of very low fat meals. The Sponsor stated their continued preference to dose the product with meals in Phase 3, but to exclude the use of a very low-fat diet. The Division stated that the differences in exposure based upon changes in fat in the diet appeared clinically significant. The Division expressed concern related to any restriction on composition of meals in Phase 3. Based upon the Division's reluctance to accept any restriction on diet in Phase 3, the Sponsor agreed that they would not restrict the type of meals consumed during Phase 3, including pre-dose meals on pharmacokinetic (PK) sampling days. However, the product would not be taken on an empty stomach.

The Division clarified that the reduction in the target range for T Cavg (see response 2a to question #1) meant narrowing the target range for the primary endpoint. Adjustments to the titration criteria may also be needed to achieve such a new primary endpoint. The Division explained that this was to ensure that patients who changed their diet for an extended period would not be exposed to high or low T concentration. The Sponsor did not agree to this proposal to narrow the target T Cavg. Instead, the Sponsor stated that their agreement to not control the fat content of meals in Phase 3 would help capture the variability in T concentrations resulting from different meal compositions and that an occasional change in meal type would not lead to adverse reactions. The Sponsor also proposed to conduct a long term (at least 1 year) safety study to assess safety of the product. As part of the safety study, the Sponsor would assess the T pharmacokinetic profile after 1 year of treatment to ensure that different meal compositions consumed during the year of treatment resulted in no significant deviations in T concentrations over the year. The Sponsor proposed that for patients who will be switching meal types on an extended basis, it could be addressed via labeling recommendations (i.e., re-titration). Based upon this discussion, the Division indicated that it would reconsider its recommendation to narrow the target T Cavg and would provide a final response in the meeting minutes.

- *Post meeting Comment: The Division has reconsidered our recommendation to narrow the target range for the T average concentration primary endpoint. With the agreements outlined above, the Division agrees that it is reasonable to use the standard, normal range as the target range for T Cavg (i.e., 300 – 1000 ng/dL) in*

the phase 3 study.

Question # 2

Clarus proposes that a single Phase III pivotal study of 12 months duration (i.e., 90-day efficacy time point and 12-months safety assessment) form the basis of an NDA submission. Is this acceptable?

Response: No. Data from a long-term safety study is needed as part of the original NDA to assess the clinical significance of the elevated serum DHT concentrations and supraphysiologic DHT/T ratios observed in Phase 2 development. We are currently considering that 24 months of safety data be submitted with the NDA and that a concurrent control group (e.g., testosterone gel) be part of the Phase 3 study. We are considering broaching this issue with external advisors and may need to obtain guidance from our Advisory Committee prior to a final recommendation to you.

Additional Discussion: The Sponsor felt that there was no need to go to an Advisory Committee at this time, although an Advisory Committee meeting might be reasonable sometime later in the process. The Sponsor reiterated their belief that a 1 year safety study, with 1 year postmarketing extension was sufficient. The Sponsor agreed to consider an active-controlled Phase 3 study, with pre-defined safety comparisons. The Division agreed to consider the Sponsor's proposal of a 1 year, active-controlled, Phase 3 study, with a 1 year postmarketing extension.

- **Is N=180 (to complete 150 subjects) adequate?**

Response: The number of subjects is adequate for an efficacy assessment, but would be insufficient for long-term safety as stated above.

Additional Discussion: The Division had considered a larger number of subjects for the safety component of the Phase 3 trial. Nonetheless, the Division recommended that Sponsor propose specific cardiovascular biomarker(s) and comparisons between groups (standard T replacement versus the Clarus product) for the CV markers and hemoglobin/hematocrit levels; the sample size for the safety component of the Phase 3 study will be determined in large part based upon the pre-defined safety endpoints and between-group comparisons.

- **Are visit schedule and safety assessments proposed for the pivotal trial and safety follow-up study acceptable?**

Response: The visit schedule and safety assessments are reasonable. Any final long-term safety protocol will need to include cardiovascular and prostate-related safety assessments and between-group comparisons in at least a 24-month study. Additional specific monitoring recommendations may be forthcoming after completion of our internal discussions.

Additional Discussion: Refer to Additional Discussion under Question #1.

- **Is the proposed dose titration scheme (based on a single blood sample drawn approximately six hours after dosing) acceptable?**

Response: Based on the summary submitted in your meeting package, the proposed titration based on sampling at 6 hours post dosing appears reasonable.

Additional Discussion: The Division stated that allowing subjects to come in from 4-6 hours post-dosing appears reasonable (Refer to Question #5).

In regard to the titration scheme, we have the following concerns:

- You propose dose titration on Days 42 and 74, based upon single blood draws from Days 30 and 60, respectively. A patient with 2 titrations would be on his final titrated dose for just 16 days prior to the primary efficacy assessment on Day 90. The titration scheme should be revised to ensure that each patient is on their final titrated dose for a minimum of 30 days.

- The titration criteria for the first and second titrations are different, with the criteria for the second titration being more complex. We have concerns that this complicated scheme may not be feasible in clinical practice.

Question # 3

Please refer to March 23rd Memorandum of Meeting Minutes (page 4) regarding FDA's position that the lower bound of a two-sided 95% confidence interval not be below 65% relative to efficacy. Clarus maintains that this requirement is overly restrictive (e.g., why a 95% CI v. 90% CI?; what is the rationale for 65%?). The Division stated that they needed to look at the historical data and discuss the 65% requirement.

Has the Agency completed their analysis and, if so, does the Division continue to recommend this specific criterion?

Response: For a point estimate of at least 75% of subjects having a testosterone C_{avg} within the normal range (300 to 1000 ng/dL), we believe that a lower bound of 65% is both clinically and statistically justified in order to maintain the precision of the point estimate. A wider interval (associated with large variance), with a possibility of the lower bound falling below 65%, is neither clinically justified nor statistically robust, for making a reasonable conclusion about efficacy, based upon a single clinical trial. In addition, sufficient descriptive data from a single uncontrolled study is needed to minimize variability in the point estimate. We generally recommend a 97.5% confidence interval to limit the false positive error rate below 2.5%, rather than a 95% confidence interval. Nonetheless, achievement of a lower response or a wider confidence interval than recommended will be a review issue.

Additional Discussion: The Sponsor agreed with the Division's response and will accept a lower bound of a two-sided 95% confidence interval not below 65% for the assessment of efficacy.

Question # 4

Clarus intends to conduct a safety follow-up that will track subjects who complete the Phase III study for an additiona1 12 months while on Clarus's oral TU product. This will

provide FDA with up to 24-month safety data in a substantial number of hypo-gonadal men. Data will be provided to FDA on a rolling basis.

Is this approach acceptable to FDA as a means to address its request for long-term (i.e., 24-month) safety data?

Response: No. Long-term safety data, as discussed in our response to Question 2, will need to be submitted in the original NDA to address the potential risks of elevated serum DHT concentrations and supraphysiologic DHT/T ratios.

Additional Discussion: The Sponsor agreed to consider an active-controlled Phase 3 study. The Division agreed to consider a 1 year, active-controlled safety study, followed by a 1 year postmarketing extension during which the study remained controlled and blinded. The Division stated that a concurrent control group would be crucial in assessing whether the Clarus product was worse than standard T replacement in terms of potential DHT-related adverse reactions such as increases in hemoglobin/hematocrit, adverse effects on serum lipids, and other CV biomarkers.

Question # 5

We believe the proposed Phase III study will yield sufficient data to validate the six hour post-dose single T sample for dose titration. Presumably, if this time point changes slightly based on the Phase III dataset, FDA will be amenable to the label reflecting the Phase III results.

Does DRUP agree?

Response: Clarify how there could be a "timepoint change" based upon the Phase 3 dataset, if the Phase 3 study is to be conducted using a 6-hour, single T sample for titration.

We remind you that labeling will be considered as part of the NDA review. It is premature at this time to provide a response to your specific labeling question.

Additional Discussion: The Sponsor clarified that the phase 3 study will be titrated based on a single time point at 6 hours post-dose. This time point has been prospectively identified and will be validated in the phase 3 study. However, because sufficient serial samples on both sides of the 6 hour sample will also be collected, it is possible that when all of the data are analyzed that, for example, the 5-hour post-dose time point is better. The Division stated that labeling will be based on how the Phase 3 study was conducted. The Sponsor stated that the 6 hours sample will actually be captured during a window of 4 – 6 hours post dose. The Division agreed with this window and reiterated that labeling would reflect the Phase 3 study procedures.

Additional comments:

- Provide a summary of available pharmacokinetic parameter values and concentration-time profiles for testosterone undecanoate from previous studies.

  Additional Discussion: Clarus stated that TU concentration data for study 07004 have recently become available. The Division recommended that Clarus submit these results as a General Correspondence.

- We recommend that you measure testosterone undecanoate (TU) and dihydrotestosterone undecanoate (DHTU) in addition to total testosterone (T), dihydrotestosterone (DHT), and free T in the serial PK samples on Days 90 – 91. It is anticipated that there may be significant systemic exposure to TU and potentially DHTU.

  Additional Discussion: The Sponsor stated their belief that measurement of serum TU and DHTU in all subjects in Phase 3 is not feasible and not necessary. The Sponsor agreed to perform the additional PK assessment for TU and DHTU in a subset of patients in the Phase 3 study. The Division agreed to a subset, but did not agree to a specific number of subjects in that subset. The Sponsor will propose a number of subjects.

- We continue to recommend that a 24 hour profile be assessed for estradiol on Day 90 rather than the proposed assessment of estradiol for only 12 hours following the morning dose.

  Additional Discussion: The Sponsor agreed to assess the 24-hour estradiol profile on Day 90.

Sponsor's Additional Questions at the Conclusion of the Meeting:

- *The Sponsor inquired as to whether the Division would file the NDA if they were to simply proceed with an open-label study of 12-months duration. The Division stated that filing decisions are made at the time of NDA submission. The Division discouraged the Sponsor from proceeding along this path, stating that Clarus needs to consider the Division's recommendation regarding the design of their Phase 3 study, especially in regard to a concurrent active control, predefined safety endpoints, additional subjects, and no restriction on meal composition. The Division is willing to review a revised protocol synopsis.*
- *The Sponsor inquired as to whether the Division would consider a "fast track" review of an NDA for oral TU. The Division stated that the Sponsor is free to request a fast track designation at the time of NDA submission, but it is highly unlikely that that request would be granted. The Division further stated that fast track is generally applied only to products that have a substantially improved safety or efficacy profile compared to other products that are already on the market and that will most likely not be the case for the Sponsor's product.*

ACTION ITEMS
The meeting minutes will be sent to the Sponsor within 30 days.

ATTACHMENTS AND HANDOUTS
See attached

Clarus Therapeutics, Inc.
IND #78,104
Type C Guidance Meeting
February 1, 2010

Comments and clarifications regarding Draft Responses/Comments from DRUP to Clarus dated January 30, 2010.

We appreciate the Division's responses/comments to the questions posed in our briefing document. In advance of our face-to-face meeting, we thought it would be useful to identify those topics that will require: a) little or no discussion given our general agreement; b) key issues requiring further discussion.

Areas of General Agreement:

1. Question #1, Responses 2a and 2b

   Clarus agrees to perform further modeling and simulation to determine the applicability of a reduced target range for serum T Cavg. If this modeling supports a reduced upper range for serum T Cavg (i.e., we maintain a high predictive probability of successfully predicting when a subject should be titrated) then we are open to adopting this new range.

2. Question #3

   Clarus will accept a lower bound of a two-sided 95% confidence interval not be below 65% relative to efficacy.

3. Question #5

   To clarify, the 6 hour post-dose single serum T sample for dose titration has been prospectively identified and will be validated in the Phase III study. However, because sufficient serial samples on both side of the 6 hr sample will also be collected, it is conceivable that when all of the data are analyzed that, for example, the 5 hour post-dose time point is better. If so, it seems reasonable that this could be reflected in the product label.

4. Additional Comments:

   a. Clarus will provide available pharmacokinetic data for TU from previous studies. We presume this means published TU data. Is this correct?
   b. We agree to assess the 24-hour estradiol profile on Day 90

Key Issues Requiring Further Discussion

1. Agency concerns re: elevated serum DHT and DHT:T ratios (Questions #1, Response 1; Question #2; Question 4)

   a. In your response under Question #2 you state, "Data from a long-term safety study (i.e., 24 months) is needed as part of the original NDA to assess the clinical significance of the elevated serum DHT concentrations and supra-physiologic DHT/T rations observed in Phase II development."

      Question: DRUP previously communicated to Clarus on April 22, 2009 that, "…it may be possible to submit safety data after one year of therapy with follow up safety data to follow". Current DRUP stance is that 24 months of safety data will be required for NDA submission. What is the specific rationale for change in stance?

      Question: Will the FDA file an NDA based on 12 month safety data with our commitment to provide 24 month safety data as originally proposed?

   b. In your response to Question #2, you state, "Any final long-term safety protocol will need to include cardiovascular and prostate-related safety assessments…."

      Question: Is the agency requiring endpoints to be prostate and cardiovascular (CV) clinical outcomes or surrogate markers of these (e.g., PSA, prostate volume, CV biomarkers)?

   c. In your response to Question #2, you stated the agency is considering that a concurrent control group be part of the phase III study because of safety concerns re: DHT. However, such a control for safety has not been required previously for T-replacement products.

      Question: What is the specific scientific evidence forming the basis of FDA's concern re: increased serum DHT levels? Our question is based, in part, on recent compelling scientific evidence that serum DHT does not determine prostate DHT levels nor does increasing serum DHT levels increase prostate size or LUTS?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-78104	GI-1	CLARUS THERAPEUTICS INC	TESTOSTERONE T ESTERS

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

/s/

MARK S HIRSCH
03/02/2010