CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212576Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 116145

MEETING MINUTES

Astex Pharmaceuticals, Inc.
Attention: Elaine Lee
Director, Global Regulatory Affairs
4420 Rosewood Drive
Suite 200
Pleasanton, CA 94588

Dear Ms. Lee:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ASTX727.

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2019. The purpose of the meeting was to discuss the proposed upcoming NDA submission for the proposed use of ASTX727 for "the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups."

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.

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

If you have any questions, call Laura Wall, Senior Regulatory Project Manager at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	August 8, 2019 from 3:30 PM to 4:30 PM (EDT)
Meeting Location:	White Oak Building 22, Conference Room: 1311
Application Number:	116145
Product Name:	ASTX727
Indication:	proposed for the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups
Sponsor:	Astex Pharmaceuticals, Inc.
Meeting Chair:	Tanya Wroblewski, MD, Clinical Team Leader
Meeting Recorder:	Laura Wall, MS, APHN-BC, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Clinical Team Leader
Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Reviewer
Laura Wall, MS, APHN-BC, Senior Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Guoxiang (George) Shen, PhD, Clinical Pharmacology Team Leader
Runyan Jin, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics V
Laura Fernandes, PhD, Biometrics Reviewer

Division of Hematology Oncology Toxicology (DHOT)
Michael L. Manning, PhD, Pharmacologist

Office of Surveillance and Epidemiology (OSE)
Brad Moriyama, DRISK Reviewer

SPONSOR ATTENDEES

Mohammad Azab, MD, MSc, President and Chief Medical Officer
Harold Keer, MD, PhD, Senior Vice President, Clinical Development
Charles LaPree, Vice President, Global Regulatory Affairs
Yong Hao, MD, PhD, Vice President, Biostatistics and Data Management
Aram Oganesian, PhD, Vice President, Clinical Pharmacology and Nonclinical
Jeanette Hale-Gates, Senior Director, Medical Writing
Elaine Lee, Director, Global Regulatory Affiars
Stefan Ochalski, PhD, Vice President, Regulatory Affairs

1.0 BACKGROUND

The purpose of the meeting was to discuss the proposed upcoming NDA submission for the proposed use of ASTX727 for "the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups." ASTX727 is administered as one ASTX727 FDC tablet (100 mg cedazuridine and 35 mg decitabine) orally once daily for 5 consecutive days (Days 1-5) of each 28-day cycle.

2.0 DISCUSSION

2.1. Regulatory

Question 1: *Does the Agency agree that a 505(b)(1) type New Drug Application is appropriate?*

FDA Response to Question 1:
It appears as if your proposed application may rely upon the Agency's finding of safety and effectiveness for NDA 021790 for Dacogen (decitabine). You note Astex Pharmaceuticals, Inc. is a subsidiary of Otsuka Pharmaceuticals. If Astex has right of reference to cross-reference NDA 021790 for Dacogen, then a 505(b)(1) application appears to be acceptable.

If at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference for use, it would be considered a 505(b)(2) NDA.

Discussion: **None.**

2.2. Clinical

Question 2: *Does the Agency agree the collective clinical package is sufficient to permit a substantive review of the NDA?*

FDA Response to Question 2:
The determination as to the submission being sufficient to permit a substantive review will be made during the filing review.

Please address the following comments regarding clinical package:

- (b) (4)
- Please specify the submission timeline of the results of the renal impairment study with respect to the NDA submission.
- Please also see response to question 8 regarding QTc study.

Discussion: **The Agency and the Sponsor discussed the additional PK analysis provided in the response. The Agency's determination as to whether or not a gastric PH study is needed will be a review issue.**

Regarding the renal impairment study, the Agency recommended that the Sponsor conduct this study in cancer patients with ASTX727. However, the Agency also agreed that the population PK analysis based on patients with mild to moderate renal impairment pooled from Phase 1/2 and Phase 3 studies may be useful to assess the effect of renal impairment on exposure of cedazuridine and decitabine. Ultimately, the need for a renal impairment study in cancer patients will be a review issue.

Question 3a: *Does the Agency agree with the studies to be included in the SCE?*

FDA Response to Question 3a:
Your approach to include phase 2 results of ASTX727-01 and preliminary results from ASTX727-02 without pooling in the SCE is acceptable.

Discussion: **None.**

Question 3b: *Does the Agency agree with the location of the text portion of the ISE?*

FDA Response to Question 3b:
The inclusion of the text portion of the ISE in the SCE is acceptable.

Discussion: None.

Question 4a: *Does the Agency agree with the pooling strategy for the ISS?*

FDA Response to Question 4a:
The approach of pooling safety by the final combination dosing is acceptable. Due to the crossover design of the phase 3 study, safety should also be presented by study drug compared to decitabine for the first two cycles.

Discussion: None.

Question 4b: *Does the Agency agree with the studies to be included in the summary of clinical safety?*

FDA Response to Question 4b:
The studies to be included in the SCS are acceptable.

Discussion: None.

Question 4c: *Does the Agency agree with the location of the text portion of the ISS?*

FDA Response to Question 4c:
The inclusion of the text portion of the ISS in the SCS is acceptable.

Discussion: None.

Question 5: *Does the Agency agree with the proposed subset of safety narratives?*

FDA Response to Question 5:
We do not agree with your plan for safety narratives. Narratives should be included for all deaths on study within 30 days of the last dose of study drug. When the cause of death is listed as disease-related, ensure that the narrative clearly describes the data showing active leukemia.

Discussion: None.

Question 6: *Does the Agency agree with the proposed format, content, and organization of datasets and SAS programs?*

FDA Response to Question 6:

The proposed datasets and programs are acceptable. Please also include the following response and death datasets, or ensure the information is included in the ADSL:

For all patients, include an integrated data file for all subjects with at least the following information:

- Study identification number, site identification number, unique subject number, treatment arm, demographic information, date of start of study drug, date of last study drug, study day of last study drug
- Best response, date of best response, study day of best response, time to best response, date of relapse, study day of relapse, time from best response to relapse
- Date of last platelet transfusion, study day of last platelet transfusion, date of last RBC transfusion, study day of last RBC transfusion
- Values for the following on the date of achievement of best response: hemoglobin, platelet count, ANC, bone marrow blasts
- Include the following baseline information: hemoglobin, platelet count, ANC, bone marrow blasts
- Date of transplantation if performed after study therapy, study day of transplantation
- Date of deaths, study day of death, date of last contact, study day of last contact, status at last contact (alive, dead or lost)

Include a death file with at least the following information:

- Study identification number, site identification number, unique subject number, treatment arm, demographic information, date of start of study drug, date of last study drug, study day of last study drug
- Date of death, time to death, proximate cause of death, root cause of death as determined by the sponsor (e.g. disease progression, adverse event, intercurrent condition, etc.)

Discussion: The Agency agreed with the Sponsor's proposal.

Question 7: *Does the Agency agree with the proposed plan regarding the long-term safety data for subjects still ongoing treatment in ASTX727-01 and ASTX727-02?*

FDA Response to Question 7:
Safety information should be provided from the ongoing trials with a data cutoff within 6 months of submission of the NDA. You should also plan on submitting a 120-day safety update during the NDA review.

Discussion: The Agency agreed with the Sponsor's proposal.

2.3. Clinical Pharmacology

Question 8: *Does the Agency agree with this alternate strategy for evaluation of QT interval prolongation from ASTX727 and that it is not necessary to conduct a thorough QT/QTc study?*

FDA Response to Question 8:
No, we do not agree with your proposed assessment because the ECG collection times do not allow for characterizing the QTc interval. Furthermore, the PK/ECG data from ASTX727 do not support the proposed concentration-QTc analysis because you did not collect an appropriate pre-treatment/baseline ECG measurement, the exposure range is too narrow to support the assessment, and the sparse sampling schedule does not allow an evaluation of any delay effects (e.g, PK/PD hysteresis).

You will need to evaluate the effect of ASTX727 on the QTc interval in an ongoing or future clinical study. Alternative study designs to the conventional 'thorough QT' study may be appropriate for this product where administering placebo and positive controls to patients is not feasible (see ICH E14 Q&A (R3) 6.1). In addition, we recommend that you incorporate the following recommendations into the QT assessment:

1) Collect high-quality ECGs which includes standardized subject handling to reduce heart rate variability and collect replicate, digital ECGs using the same model of calibrated ECG machine for each subject.
2) Submit a protocol with detailed statistical analysis plan including primary analysis, sample size justification, secondary analysis, and categorical analysis to further evaluate the adequacy of your proposed QT evaluation.
3) If you propose to conduct concentration-QTc analysis, we recommend the analysis and reporting of results follow the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

Discussion: **The Agency clarified that the current data would not be sufficient to support the QT assessment of ASTX727. The Agency recommended that the Sponsor include a rationale and discussion as to why the decitabine experience does not suggest a QT prolongation concern in addition to submission and discussion of the cardiac and ECG data in the phase 3 study with the NDA submission. The Agency discussed that a QT study in healthy volunteers with cedazuridine would be required as a postmarketing requirement. The Agency recommended that the Sponsor submit a proposal for this study for the Agency to review.**

2.4. Nonclinical

Question 9: *Does the Agency agree that the collective nonclinical package is sufficient to permit a substantive review of the NDA?*

FDA Response to Question 9:
The Agency agrees your nonclinical development program appears adequate to support filing an NDA; the adequacy of your studies will be a review issue. Your NDA submission should include a scientific justification for not conducting chronic toxicology studies for the cedazuridine and decitabine combination.

Discussion: **None.**

Question 10: *Does the Agency agree with the proposed format for submission of nonclinical study reports and trial summary datasets?*

FDA Response to Question 10:
The Agency agrees with your proposal.

Discussion: **None.**

2.5. Labeling

Question 11a: *Does the Agency agree with the proposed indication statement for ASTX727 if the NDA is deemed approvable?*

FDA Response to Question 11a:
Discussion of the proposed indication will be a review issue.

Discussion: **None.**

Question 11b: (b) (4)

FDA Response to Question 11b:

(b) (4)

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(b) (4)

Discussion: **None.**

Question 12: *Does the Agency agree with the plan to include efficacy and safety information from the ASTX727 clinical program in the USPI?*

FDA Response to Question 12:
Efficacy and safety information from the trials of ASTX727 should be incorporated into the USPI.

Discussion: **None.**

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that a REMS is not necessary.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

SECURE EMAIL COMMUNICATIONS

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major

trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[8]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[9]

Discussion: The Agency discussed the Assessment Aid with the Sponsor and provided a copy of the template of the Assessment Aid to the Sponsor after the meeting.

The Sponsor intends to participate in the Assessment Aid pilot project and plans to submit Assessment Aid within 30 days of the application submission.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

[7] https://www.fda.gov/media/85061/download
[8] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[9] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor submitted the attached responses to the Agency's meeting preliminary comments via e-mail on August 6, 2019.

25 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

TANYA M WROBLEWSKI
08/19/2019 10:41:43 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116145

MEETING MINUTES

Astex Pharmaceuticals, Inc.
Attention: Ruth Ryan Lessard
Senior Director, Regulatory Affairs
4420 Rosewood Drive, Suite 200
Pleasanton, CA 94588

Dear Ms. Lessard:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ASTX727.

We also refer to the teleconference between representatives of your firm and the FDA on March 20, 2017. The purpose of the meeting was to discuss data from the phase 1/2 studies and to seek Agency advice on the design of a pivotal study in myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML).

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

If you have any questions, please call Kelly Miller, Regulatory Project Manager, at (240) 402-6613.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: March 20, 2017, 3:00PM-4:00PM ET
Meeting Location: Teleconference

Application Number: IND 116145
Product Name: ASTX727
Indication: Myelodysplastic syndrome and chronic myelomonocytic leukemia
Sponsor/Applicant Name: Astex Pharmaceuticals, Inc.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Kelly Miller, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, Medical Officer
Ashley Ward, MD, Medical Officer
Kelly Miller, RPh, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Michael Manning, PhD, Pharmacologist

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Brian Booth, PhD, Deputy Director
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V
Yuan-Li Shen, DrPh, Team Leader
Yaping Wang, PhD, Statistical Reviewer

SPONSOR ATTENDEES

Mohammad Azab, MD, MSc, President & Chief Medical Officer

Sam Kim, Senior Director, Project Management
James Lowder, MD, Executive Director, Clinical Research & Medical Monitor
Ruth Ryan Lessard, Executive Director, Regulatory Affairs
Chester (Chihche) Lin, PhD, Senior Manager, Biostatistics
Aram Oganesian, PhD, DABT, Executive Director, Clinical Pharmacology & Non-Clinical Development
(b) (4)

1.0 BACKGROUND

Astex has completed a Phase 1-2 study (ASTX727-01) that examined the exposure for each component of ASTX727 and determined a combination dose that emulates the pharmacokinetics of IV decitabine for AUC over 5 days of dosing, and pharmacodynamics as measured by long interspersed nuclear element-1 (LINE-1) demethylation after 5 days of dosing.

The purpose of the meeting is to obtain FDA feedback on the design of a single Phase 3 clinical trial for the treatment of higher risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) to support (along with data obtained in ASTX727-01) registration of ASTX727. Both ASTX727-01 and the proposed Phase 3 study (ASTX727-02) employ a randomized design to compare with IV decitabine but with different primary endpoints: ASTX727-01 used an intrasubject crossover design to provide data to support that mean AUC and DNA demethylation achieved by ASTX727 are similar to IV decitabine at the approved dose and schedule, whereas the Phase 3 study will (b) (4) . Astex seeks FDA advice on the design of the Phase 3 study, ASTX727-02, and the non-clinical and clinical pharmacology data intended for the NDA. Astex intends to initiate the ASTX727-02 trial in 2017.

FDA sent Preliminary Comments to Astex Pharmaceuticals, Inc. on March 15, 2017.

2.0 DISCUSSION

Question 1:
Astex will be seeking an indication statement similar to the currently approved US Prescribing Information for Dacogen (decitabine IV) for the 5-day regimen. Does FDA agree the eligibility criteria for the proposed Phase 3 trial adequately reflect the decitabine IV indication statement and support a similar indication for ASTX727?

FDA Response to Question 1:
We do not agree with your study design. Refer to responses below.

Discussion:
See discussion for Question 3.

Question 2:

(b) (4)

FDA Response to Question 2:

No. We recommend you make decitabine AUC as the primary endpoint. You may use literature and your own internal data to justify the use of decitabine AUC as a primary endpoint.

(b) (4)

Discussion:

See discussion for Question 3.

Question 3:

(b) (4)

FDA Response to Question 3:

No. We recommend that you consider a pharmacokinetic-bridging approach to establish the safety and effectiveness of ASTX727-02 based on bridging to the clinical pharmacology data for Dacogen.

We recommend a parallel study design in patients using decitabine AUC equivalence as the primary endpoint (i.e., 90% CI intervals of the GMR for equivalence). The margin for equivalence and sample size need to be justified.

The primary efficacy analysis should be based on ITT population.

In a trial with a primary endpoint of AUC, the clinical endpoints will be descriptive only. In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints cannot result in (either singly or in combination) a claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label.

Please note that the number of patients not being evaluated for the primary and key secondary endpoints should be kept to a minimum. Too much missing data will undermine the reliability and confidence of the results. Sensitivity analyses should be performed to examine the potential impact of the missing data. For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955. A special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730.

Discussion:

The Agency provided clarification that the approach for establishing safety and effectiveness of ASTX727 would be based primarily on a pharmacokinetic bridging approach as described in the 1998 FDA Guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" available at https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf.

The Agency would consider either a parallel or cross-over randomized design with a primary endpoint of cycle 1 and cycle 2 AUC. The Agency recommended that the Sponsor submit sample size calculations and supporting assumptions to support the sample size of either design.

Regarding treatment after cycle 2, the Agency has no objections with continuation of patients with oral ASTX727 with the caveat that this data will be mainly used for descriptive purposes.

Regarding the definition of the analysis population for the primary endpoint, the Agency recommended that the Sponsor provide details of the approach and definition of which patients will be included in the primary analysis population. The Agency notes that the amount of missing data will be a review issue.

Question 4:

Does FDA agree with the plan for provision of data from ASTX727 Clinical Pharmacology studies for E7727 and the FDC at the time of NDA submission?

FDA Response to Question 4:
Your approach appears acceptable; however we are recommending major changes with your overall clinical development program (see response to Question 3).

Using available data provide justification for the proposed fixed dosing of ASTX727. This justification should be included in your planned pivotal trial protocol.

In addition, in Study ASTX727-01, it appears that the 35 mg decitabine dose in ASTX727 leads to consistently lower decitabine AUC and demethylation levels. Prior to initiation of your pivotal trial, you should ensure that your fixed combination for ASTX727 achieves similar decitabine AUC and demethylation levels as IV decitabine to meet equivalence testing.

Discussion

(b) (4)

The Sponsor agreed to re-examine the PK and PD data to support the proposed ASTX727 dose for the proposed randomized trial.

Question 5:
Astex has data characterizing the nonclinical safety of E7727. The dose of E7727 selected for the FDC is ~40-fold below the NOAEL determined in the IND enabling toxicity study. The safety profile of IV decitabine is well established, and Astex has completed single-cycle toxicology studies with oral decitabine in 2 species. Does FDA agree the data package and additional planned nonclinical studies for E7727 are sufficient?

FDA Response to Question 5:
Assuming there are no changes in the emerging safety profile of ASTX727, the FDA agrees your completed and planned nonclinical studies for E7727 appear sufficient to support filing an NDA; the results of these studies will be a review issue. Your NDA should include a scientific justification for not conducting a dedicated chronic toxicology study of the combination.

Discussion:
No discussion occurred.

Question 6:
Astex will provide pivotal data from both the Phase 1-2 study (ASTX727-01), which included a randomized crossover design with decitabine IV for PK and PD similarity, and the proposed Phase 3 study (ASTX727-02) (b) (4) *Does FDA agree that these clinical data provide the basis for submission of an NDA seeking approval of ASTX727 for treatment of MDS and CMML with an indication statement similar to decitabine IV?*

FDA Response to Question 6:
It is premature to respond to this question given the major changes recommended for your clinical development program.

Discussion:
The Agency recommends submission of a pre-NDA meeting request once topline PK/PD, efficacy, and safety data are available from the pivotal and supportive trials.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SECURE EMAIL COMMUNICATIONS

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Slides from the Sponsor are attached.

4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

ROMEO A DE CLARO
03/24/2017