

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219083Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 138814

MEETING MINUTES

Cytokinetics, Inc.
Attention: Rachel E. Melman, MBS, RAC
Senior Director, Regulatory Affairs
350 Oyster Point Blvd
South San Francisco, CA 94080

Dear Rachel Melman:

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

We also refer to the video conference between representatives of your firm and the FDA on February 26, 2024. The purpose of the meeting was to discuss and obtain feedback and agreement on the proposed questions on outstanding administrative, regulatory, quality, nonclinical, and clinical questions for the purposes of pursuing a new drug application (NDA) for aficamten.

A copy of the official minutes of the video conference 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 Maryam Changi, Regulatory Project Manager at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Slides



MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: February 26, 2024; 12:00 pm to 1:00 pm ET

Meeting Location: Videoconference

Application Number: IND 138814

Product Name: Aficamten

Indication: The treatment of adults with symptomatic obstructive hypertrophic cardiomyopathy (oHCM)

Sponsor Name: Cytokinetics, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Norman Stockbridge, MD, PhD

Meeting Recorder: Maryam Changi, PharmD

FDA ATTENDEES

Division of Cardiology and Nephrology

Norman Stockbridge, MD, PhD, Director
Aliza Thompson, MD, MS, Deputy Director
Mary Ross Southworth, PharmD, Deputy Director for Safety
Michael Monteleone, MS, RAC, Associate Director for Labeling
Fortunato Senatore, MD, PhD, FACC, Clinical Team Leader
Charu Gandotra, MD, Clinical Reviewer
Tzu-Yun McDowell, PhD, Clinical Reviewer

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology:

Alexis Childers, RAC, Chief, Project Management Staff
Maryam Changi, PharmD, Sr. Regulatory Health Project Manager

**Office of Biostatistics, Division of Biometrics III*

Jennifer Clark, PhD, Team Leader
Ququan (Cherry) Liu, MD, MS, Statistician

**Office of Clinical Pharmacology; Division of Cardiometabolic and Endocrine Pharmacology:*

Doanh Tran, PhD, Deputy Director
Li Wang, PhD, Clinical Pharmacology Reviewer

**Division of Risk Management:*

Laura Zendel, PharmD, Deputy Director
Brian Caruth, PharmD, BCPS, Risk Management Analyst
Yasmeen Abou-Sayed, PharmD, Team Leader

** Division of Pharmacology & Toxicology-Cardiology, Hematology, Endocrinology, and Nephrology:*

Andrew Jacob, PhD, Reviewer

**Office of Product Quality:*

Theodor Carver, PhD, CMC Team Leader
Jennifer McCord, PhD, CMC Reviewer

SPONSOR ATTENDEES

Robert Blum, President and Chief Executive Officer
Camelia Dumitrescu, MD, MPH, Head of Drug Safety and Pharmacovigilance
Polina German, PharmD, Head of Clinical Pharmacology
Justin Lutz, PharmD, PhD, Director, Clinical Pharmacology
Stephen Heitner, MD, Vice President, Clinical Research & Therapeutic Lead,
Cardiovascular
Victoria Herbert, MS, Associate Director, Regulatory Affairs
Daniel Jacoby, MD, FACC, Senior Medical Director, Clinical Research, Cardiovascular
Stuart Kupfer, MD, Senior Vice President, Chief Medical Officer
Fady Malik, MD, PhD, FACC, FHFA, HFSA, Executive Vice President, Research &
Development
Rachel Melman, MBS RAC, Senior Director, Regulatory Affairs
Lixin (Lisa) Meng, PhD, Vice President, Biometrics
Christine Murray, MS, Senior Vice President, Regulatory Affairs & Quality
Michael Pugsley, PhD, FBPhS, DSP, Senior Director, Safety Pharmacology and
Toxicology
Norma Tom, PhD, Vice President, CMC
Qi (Amy) Wohltman, ME, Senior Director, Biostatistics

1.0 BACKGROUND

Aficamten (CK-3773274) is a small molecule, allosteric inhibitor of cardiac myosin. Cytokinetics, the Sponsor, is developing aficamten for once daily chronic oral administration for the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM) and symptomatic non-obstructive hypertrophic cardiomyopathy (nHCM). Aficamten received Orphan Designation in January 2021 for the treatment of symptomatic hypertrophic cardiomyopathy. Aficamten also received breakthrough designation on December 6, 2021.

The Division met with Cytokinetics several times throughout development, including an End-of -Phase 2 meeting held on April 26, 2023, where the planned phase 3 trial, CY 6033, intended to evaluate the efficacy and safety of aficamten compared to placebo in adults with symptomatic nHCM was discussed.

A Topline Meeting was held on February 8, 2024, where the Sponsor presented the results from the pivotal phase 3 trial, CY 6031 (SEQUOIA-HCM), and the long-term extension trial CY 6022 (FOREST-HCM). These trials, in addition to the phase 2 trial (REDWOOD), are expected to form the basis of the NDA for aficamten to improve peak oxygen uptake (i.e., exercise capacity) in patients with obstructive hypertrophic cardiomyopathy (oHCM).

The purpose of this meeting was to discuss and obtain feedback and agreement on the proposed questions on outstanding administrative, regulatory, quality, nonclinical, and clinical questions for the purposes of pursuing an NDA for aficamten.

2.0 DISCUSSION

2.1. Quality

Question 1: *Does FDA agree the CMC package is sufficient to support the NDA for aficamten?*

FDA Response:

We do not agree, because we note that information required to be in Module 3 is omitted, including descriptions of the controls (and associated justifications) for the drug substance and drug product, and stability protocols for the drug substance. Refer to ICH M4Q(R1), the ICH quality guidelines, and 21 CFR 314.50 for general guidance regarding CMC information to be included in the NDA. The completeness and adequacy of the CMC information will be an issue for review of the NDA.

Meeting Discussion:

The Sponsor stated that they will include the comprehensive control strategy, the associated justification, and their stability protocol in the Module 3. The Sponsor further explained that the control strategy for the drug product will be based on completed studies and will include specifications for the excipients and the drug product. The Division agreed with the Sponsor's plan in principle.

Question 2: *Does FDA agree with the revised proposal for the drug product stability data package that will submit 12 month stability data for 1 batch at the time of the NDA submission and for 2 of 3 batches prior to the end of the 60-day filing review period?*

FDA Response:

We do not agree with your proposal to submit less than 12 months of long-term stability data for drug product lots at the time of NDA submission. The Agency's expectation is that at least 12 months of long-term stability data for 3 primary batches will be provided at the time of the initial NDA submission, in accordance with recommendations in the ICH Q1A(R2) guideline.

Meeting Discussion:

The Sponsor provided their rationale for requesting (b) (4) stability data and stated they will provide 12 months registration stability batches for phase 2 and 3 by day 60 of the NDA submission. The Division explained that in general 12 months stability data are requested to identify any trending. In consult with clinical team, it was determined that while the product had been granted a Breakthrough Therapy Designation, there was no medical necessity identified to allow (b) (4) months of long-term stability data. Thus, the Division did not agree with the Sponsor's proposal to submit (b) (4) months of long-term stability data.

2.2. Non-Clinical

Question 3: *Does FDA agree the nonclinical package is sufficient to support the NDA for aficamten?*

FDA Response:

Your nonclinical package appears sufficient to support submission of the NDA for aficamten. The 2-year carcinogenicity study is usually expected at the time of NDA filing. Considering the seriousness of the condition that aficamten intends to treat and a preliminary risk assessment based on available nonclinical data, we agree that the 2-year rat carcinogenicity study can be completed post-approval and the final study report be submitted as soon as it is available, no later than the 120-day Safety Update date.

Meeting Discussion:

The Sponsor acknowledged the response. No additional discussion.

2.3. Clinical

Question 4: *Does FDA agree that the clinical pharmacology package for aficamten is sufficient to support an NDA?*

FDA Response:

We note that you have not investigated the impact of renal impairment on PK of aficamten. As aficamten is predominantly eliminated via metabolism, we recommend you conduct a reduced study to evaluate the impact of severe renal impairment on the PK of aficamten. Refer to Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing regarding study design and data analysis.

Meeting Discussion:

The Sponsor asked the rationale for the request for data from a dedicated renal impairment study. The Division explained that the recommendation was based on the referenced guidance where a reduced study in subjects with severe renal impairment is recommended for drugs that are primarily cleared via metabolism. The sponsor noted that there are not many patients with severe renal impairment that would need to use this drug. They also noted that this drug will be titrated so the main concerns would be whether the starting dose would be appropriate for patients with severe renal impairment. The Division stated to include the rationale with supporting data that there will be limited use in patients with severe renal impairment. The Sponsor should also conduct analysis to assess the impact of a potential decreased clearance due to severe renal impairment on the safety of the starting dose. The Division clarified this is unlikely to be a filing issue.

Question 5: *Does FDA agree that the elimination of aficamten has been sufficiently characterized to support provision of dosing guidance with respect to co-administration of other medications in the USPI?*

FDA Response:

Whether the elimination profile and drug-drug interaction (DDI) risk of aficamten has been sufficiently characterized based on the in vitro and clinical data will be a review issue at the time of NDA submission. We note that the dosing regimen of fluoxetine was 20 mg QD for 7 days, then 40 mg fluoxetine QD for 27 days in Study CY 601-10. In three reported clinical DDI studies, the dose of fluoxetine was selected as 60 mg to exert maximum inhibition on CYP2C19 activity (PubMed 21877765, PubMed 24688155, and PubMed 24569517). Provide justification on dose selection

of fluoxetine as a strong CYP2C19 inhibitor in Study 601-10 when submitting the NDA package.

Meeting Discussion:

None.

Question 6: *Does FDA agree the proposed clinical package characterizing the efficacy and safety of aficamten in patients with symptomatic oHCM is sufficient to support an NDA?*

FDA Response:

The proposed clinical package appears to be sufficient to support submission of an NDA for aficamten for the treatment of oHCM. We noted that the preliminary safety findings for the open label, long-term extension study CY 6022 only summarize the results from the newly enrolled patients in the study. The long-term safety profile of patients rolling over from the phase 2 and 3 studies in study CY 6022 should be evaluated and summarized in your NDA package.

Meeting Discussion:

The Division stated that the proposed plan for safety analyses appears to be reasonable. The Division requests the Sponsor to provide the exposure adjusted incidence rate for adverse event of special interest such as LVEF <50% from the open-label extension study as well as the phase 3 trial. The Division also asked the Sponsor to further clarify the headings/numbers in Table 42, in the briefing package, with regard to the estimated cumulative exposure in the briefing document.

Question 7: *Does FDA agree that the proposed CRF and patient narratives strategies are sufficient to support the NDA for aficamten?*

FDA Response:

Yes, we agree. Please note that CRFs must include all clinical documents collected regardless of whether you label them as “CRFs” (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

Meeting Discussion:

None.

Question 8: *Does FDA agree that the BIMO listing approach of “By Site, by Subject Profile Option B” is sufficient to support the NDA for aficamten?*

FDA Response:

Yes, we agree with the Option B formatting in Figure 4 for the PDF of subject-level data line listings provided for each study used to support safety and efficacy in the NDA.

Meeting Discussion:

None.

Question 9: *Does FDA agree with the updated proposed SDSP for the NDA for aficamten?*

FDA Response:

The proposed SDSP is acceptable. Please provide all code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and phase 3 trial clinical study report.

Meeting Discussion:

None.

2.4. Administrative

Question 10: *If the 12-month stability drug product data are rate-limiting for the submission of the NDA for aficamten, is FDA willing to accept a rolling review of the NDA for aficamten with the clinical and nonclinical modules submitted ahead of the full NDA?*

FDA Response:

We will accept a rolling review with the clinical and nonclinical modules ahead of the full NDA submission.

Meeting Discussion:

None.

Question 11: *Does FDA support the proposal of priority review status for the NDA for aficamten?*

FDA Response:

We agree that aficamten is intended to treat a serious condition. We note that aficamten may have a better PK/DDI profile compared to the available therapy. However, a cross-study comparison is not sufficient to demonstrate that aficamten would provide a significant improvement in effectiveness or safety over the available therapy. The clinical impacts of the PK/DDI will be evaluated during the NDA review. It is unlikely that priority review will be granted based on the available data.

Meeting Discussion:

The Division commented that the Sponsor outlined a reasonable list of evidence and had no recommendations on what additional information would be needed for the justification for a priority review. The Division stated the

decision regarding granting a priority review will be determined at the time of NDA submission.

Question 12: *Does FDA agree with the proposal for the 120-day Safety Update for the NDA for aficamten?*

FDA Response:

Your proposal seems acceptable.

Meeting Discussion:

None.

Question 13: *Does FDA agree with the proposed plan for submitting ECG waveforms for the NDA for aficamten?*

FDA Response:

Yes, we agree. Please refer to the FDA document "[Submitting ECG Waveform Data \(Frequently Asked Questions\)](#)" for additional guidance on submitting ECG waveform data.

Meeting Discussion:

None.

POST MEETING NOTES:

Question 14: *Does the FDA agree with the identification of Study CY 6031 (SEQUOIA-HCM) as the only covered clinical study for purposes of financial disclosure and certification in the planned NDA?*

Company Position

Module 1.3.4 of the planned NDA for aficamten for the treatment of symptomatic oHCM will include certification and, if applicable, disclosure of financial interests and arrangements for investigators participating in studies included in the NDA which are considered to be "covered clinical studies" in accordance with requirements described under 21 CFR Part 54 and as further described in the February 2013 FDA Guidance for Industry titled "*Guidance for Clinical Investigators Industry, and FDA Staff: Financial Disclosure by Clinical Investigators*". Cytokinetics has evaluated all clinical studies planned for inclusion in the NDA and considers the Phase 3 Study CY 6031 (SEQUOIA-HCM) to be the only covered clinical study in the planned NDA for aficamten as it serves as the basis for the primary effectiveness of aficamten.

FDA Response:

Yes, we agree.

ADDITIONAL COMMENTS:

Of note, the other currently approved cardiac myosin inhibitor has a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of heart failure due to systolic dysfunction. You are encouraged to submit a proposed REMS with your application or submit a strong rationale for why you believe a REMS is not needed and why labeling alone is sufficient to mitigate the risks of aficamten.

Meeting Discussion:

The Sponsor acknowledged the Division's comment and stated they plan to request a separate meeting prior to NDA submission to discuss the safety profile of aficamten and risk management.

2.5. Additional Requests from the Division

1. Please submit the following information at the time of NDA submission:

a. Randomization

A dataset that links the subject's randomization number and unique subject ID to the allocated medication kit/box number, medication name, and associated define file.

b. Protocol and Statistical Analysis Plan (SAP)

- 1) All versions of the protocol for SEQUOIA-HCM and the date when changes were implemented. Include a Summary of Changes for each version.
- 2) All versions of the SAP for SEQUOIA-HCM. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

c. Clinical Trial Materials

- 1) Sample clinical trial kits, from both treatment arms, identical to those used during SEQUOIA-HCM. Ship them to Ms. Maryam Changi's desk address in the same packaging as will be used for shipping to investigative sites.
- 2) All data management plans for SEQUOIA-HCM. Cite all amendments for each data management plan, including all manual and programmatic checks.
- 3) All site monitoring plans for SEQUOIA-HCM. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

- 4) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in SEQUOIA-HCM.
- 5) All charters for committees involved in conducting SEQUOIA-HCM (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.)
- 6) All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.
- 7) All newsletters and all other communications to investigational sites and national coordinators from the groups responsible for the conduct of SEQUOIA-HCM. Please bookmark the communication by date.

d. General Data and Analyses

- 1) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure.
- 2) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit code that was used to create or clean up your analysis datasets.
- 3) Subject ID variable for all open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.
- 4) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.
- 5) Dataset that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.
- 6) A table set up similarly to the dataset requested in above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission (subjects with cardiovascular events of interest, subjects with hepatic laboratory anomalies of interest, etc.).
- 7) One table which includes the following information for SEQUOIA-HCM:

- Dates of first patient and last patient visits
- Date of data lock
- Dates for each interim analysis
- Dates of all versions of the SAP (with a hyperlink to each SAP)
- Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

Other

- 1) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.
- 2) Rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS)

There are two major pieces to this applicability of foreign data issue as follows:

- Are the patients the same (US versus rest of the world)?
 - Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?
- 3) An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT MEETING LANGUAGE:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- 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.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 Information¹ and Pregnancy and Lactation Labeling Final Rule² 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
- 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

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

² <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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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.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁴. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

³ <https://www.fda.gov/media/84223/download>

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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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*.⁵

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.⁶

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁷ 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or before

⁵ <https://www.fda.gov/media/85061/download>

⁶ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁸

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 Resources⁹.

⁸ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21

CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

4.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the enclosed slides entitled: "Aficamten, For the treatment of obstructive hypertrophic cardiomyopathy (oHCM), Pre-NDA Meeting 26 February 2024" on Friday, February 23, 2024.

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

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/

NORMAN L STOCKBRIDGE
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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 138814
Request Receipt Date	October 21, 2021
Product	Aficamten (CK-3773274)
Indication	Treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM), to improve heart failure symptoms, exercise capacity, and New York Health Association (NYHA) functional class.
Drug Class/Mechanism of Action	Allosteric inhibitor of cardiac myosin
Sponsor	Cytokinetics, Inc.
ODE/Division	OCHEN/DCN
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	December 20, 2021

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

For the treatment of symptomatic obstructive hypertrophic cardiomyopathy (oHCM), to improve heart failure symptoms, (b) (4).

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Ragqio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Ragqio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Drug Product: Aficamten is a small molecule allosteric inhibitor of cardiac myosin designed to reduce cardiac hypercontractility which underlies the pathophysiology of hypertrophic cardiomyopathy (HCM). Aficamten decreases

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

the ability of myosin to bind to actin in the off-actin state, which results in decreased contractility of the myocardium. The reduction in cardiac contractile force is expected to alleviate left ventricular outflow tract (LVOT) obstruction and so have the potential to improve functional capacity and relieve symptoms in patients with obstructive HCM (oHCM).

Disease background: HCM is a genetic myocardial disorder characterized by LV hypertrophy, hyperdynamic contraction and impaired diastolic function. oHCM is a clinical phenotype where obstruction is defined as a peak LVOT gradient ≥ 30 mmHg at rest or ≥ 50 mmHg at with provocation. The pathognomic combination of septal hypertrophy and systolic anterior motion of the mitral valve leaflet caused by the LVOT obstruction results in various degrees of mitral regurgitation. The health impacts of HCM are variable with a wide range of symptom presentations and disease courses. Many patients experience minimal or few symptoms and minor or no limitations in daily activity; however, others suffer significant debilitating consequences and high symptom burden, with profound effects on their lives. The typical symptoms of HCM include dyspnea, diminished exercise tolerance, anginal chest pain, palpitations, and syncope. Patients with HCM are at high risk of developing atrial fibrillation which can further lead to stroke, heart failure and death. HCM is associated with an increased risk of sudden cardiac death in a minority of patients and can require implantable cardioverter-defibrillator (ICD) placement.

Drug's Relation to Existing Therapy: There are no currently approved disease-specific or sarcomere-targeted therapies for oHCM. Current guidelines for the pharmacologic management of HCM recommend the use of negative inotropic agents, including β -blockers, non-dihydropyridine calcium channel blockers, and disopyramide. Only the β -blocker propranolol carries an approved indication for improving NYHA functional class. Current pharmacologic treatments may improve LVOT obstruction, but they offer limited and variable relief in symptoms and functional status. In patients with oHCM, septal reduction therapy may reduce obstruction and improve LV outflow, but it involves invasive procedures including surgical myomectomy and alcohol septal ablation that carry substantial risks and may not be available to all patients. There continues to be an unmet need for a disease-specific drug to treat HCM. A brief description of available therapies is summarized in our response to item 9.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Applicant has completed a Phase 1 study (CY 6011) in 114 healthy participants and has an ongoing Phase 2 study (CY6021) to evaluate the safety, tolerability, PK and PD of aficamten in approximately 60 adults with symptomatic oHCM. The Applicant believes that data from the first two cohorts of CY 6021 provides the main preliminary clinical evidence to support their request for Breakthrough Therapy Designation (BTD).

The primary objective of CY6021 was to determine the safety and tolerability of aficamten in patients with symptomatic oHCM. The primary endpoints were safety endpoints including treatment-emergent adverse events, treatment-emergent serious adverse events and incidence of LVEF $<50\%$.

The preliminary efficacy of aficamten was assessed in several secondary and exploratory endpoints.

Secondary endpoints:

- Change from baseline in Resting and Post-Valsalva LVOT gradient (LVOT-G) at Week 10

- Proportion of patients achieving complete hemodynamic response (resting LVOT-G of <30 mmHg and a post-Valsalva LVOT-G <50 mmHg) at Week 10
- LVEF change over time

Key Exploratory endpoints:

- Change from baseline in NT-proBNP at Week 10
- Proportion of patients with improvement in NYHA Class ≥ 1

Planned primary endpoint for the Phase 3 study (CY 6031): Change from baseline in peak oxygen uptake (pVO_2) at Week 24, measured by cardiopulmonary exercise testing (CPET)

Planned secondary endpoints for the Phase 3 study (CY 6031):

- Change in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS)
- Proportion of patients with ≥ 1 class improvement in NYHA Functional Class
- Change in provoked (Valsalva) LVOT-G
- Change in total workload during CPET

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- Improvement in function. This usually involves an objective measure of exercise capacity from standardized exercise tolerance testing. pVO_2 from CPET has been used as a clinical endpoint in this class of drug.
 - Relief of symptoms leading to important improvement in patient's perception of their health status and health-related quality of life
 - Reduction in the need for invasive treatments including surgical myomectomy, alcohol septal ablation, or cardiac transplant.
 - Reduction in mortality and/or hospitalization. Mortality is unlikely to be a useful efficacy outcome because most oHCM patients with normal LV systolic function have low short- and intermediate-term risk for death.
- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.
- None

9. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

Pharmacologic Therapies

- β -blockers – have been the first line medication and mainstay of pharmacologic therapy for HCM due to their negative inotropic effects which are thought to decrease the hypercontractile state and the degree of LVOT obstruction and negative chronotropic effects (prolonging filling). Propranolol is the only approved β -blocker for the improvement of NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis (an old name for oHCM). This approval was based on an uncontrolled series of 13 patients followed for 17 months in which NYHA functional class improved for most patients.

- Non-dihydropyridine calcium channel blockers (verapamil or diltiazem)- are often used as second-line agents after β -blockers have been shown to be clinically ineffective, poorly tolerated or contraindicated. These agents also act via their negative inotropic and negative chronotropic effects, but these agents are used with caution due to their ability to worsen LVOT obstruction due to peripheral vasodilation, and they are not labeled for this use.
- Disopyramide – is used off label as add-on therapy for patients without adequate symptom relief from β -blockers or calcium channel blockers. Disopyramide is frequently poorly tolerated due to significant anticholinergic side-effects and its associated pro-arrhythmic effect (QT prolongation and heart block), a concern in oHCM patients who are at increased risk of sudden cardiac death.

Interventional therapies-Septal Reduction Therapy

- Surgical Myectomy – surgical transaortic septal myectomy, operative removal of a portion of the interventricular septum, is considered the gold-standard for severely symptomatic medically refractory oHCM patients. The results are operator-dependent and surgery is somewhat limited both by geography and expertise. Risks include infection, bleeding and the need for permanent pacemaker implantation.
- Transcatheter Alcohol Septal Ablation- is an alternative, less invasive approach to septal mass reduction in oHCM. Alcohol septal ablation involves catheter-directed infusion of alcohol directly into a coronary artery septal branch to cause a septal myocardial infarction. This procedure can result in heart block requiring implantation of a permanent pacemaker. Similar to surgical myectomy, the results are operator-dependent. The long-term effects of the resulting septal scar on arrhythmogenesis and cardiac remodeling are unknown.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Mavacamten (IND 121904, NDA 214998), an allosteric inhibitor of cardiac myosin, received a BTDR on July 22, 2020 based on data from a double-blind, placebo-controlled Phase 3 study demonstrating positive effects on both symptoms and function. The BTDR for Mavacamten was previously requested based on data from an uncontrolled, open-label Phase 2 study but not awarded. The rationale for denial was because whether the target doses of mavacamten could show a greater magnitude of reduction in LVOT gradient on top of β -blockers as compared to β -blockers alone was unknown at the time of the request.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The main preliminary clinical evidence in support of a BTDR for aficamten comes from data from the first two cohorts of the Phase 2 study (CY 6021) whose design and results are described below.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study ID	Phase	Study design	Treatment group
CY 6021 On going	Phase 2 (10 weeks treatment with a 4-week follow up period)	Multi-center, randomized, double- blind, placebo- controlled	Cohort 1 (N = 21, n = 14 aficamten [5, 10, 15 mg QD] and n = 7 placebo) Cohort 2 (N = 20, n = 14 aficamten [10, 20, 30 mg QD] and n = 6 placebo) Cohort 3 (on going)

This randomized, placebo-controlled, double-blind Phase 2 study was a dose-finding trial of aficamten in patients with symptomatic oHCM receiving standard of care medications (e.g., β -blockers). Cohort 1 and Cohort 2 of this Phase 2 study are complete. A third ongoing cohort has enrolled patients in an open-label fashion to assess aficamten in addition to standard of care background therapy that includes disopyramide.

Doses in Cohort 1 and Cohort 3 were 5, 10, 15 mg once daily; doses in Cohort 2 were 10, 20, and 30 mg once daily. The dose of aficamten or placebo image was escalated (e.g., 5→10→15 mg) based on echocardiographic guidance. Scheduled up-titration to the next level occurred every 2 weeks (Week 2, Week 4 or Week 6) if either of the following conditions were met on echocardiography:

- Resting LVOT-G ≥ 30 mmHg and the LVEF $\geq 50\%$ or
- Resting LVOT-G < 30 mmHg, post-Valsalva LVOT-G ≥ 50 mmHg, and LVEF $\geq 50\%$

Otherwise, the patient remained on the same dose. If LVEF was $< 50\%$, the patient was returned to a prior dose level or to placebo if the patients were on the lowest dose. Treatment was to be discontinued if LVEF $< 40\%$.

Baseline characteristic for patients in Cohorts 1 and 2 were summarized in the table below. The mean age was 57 years, and 34% of patients were ≥ 65 years of age. It is noted that there was a numeric imbalance in baseline NYHA class with 29% and 50% of aficamten-treated patients in Cohort 1 and Cohort 2, respectively, assessed as NYHA class III at baseline versus 15% in the combined placebo treated patients. At baseline, 85% of placebo treated patients were receiving β -blockers as compared with 64% and 79% of aficamten-treated patients in Cohorts 1 and 2, respectively.

Table 1 Demographic and Baseline Characteristics, CY 6021, Cohorts 1 and 2

Characteristics	Combined Placebo (N=13)	Aficamten		Overall (N=41)
		Cohort 1 (N=14)	Cohort 2 (N=14)	
Age (years) Mean (SD)	57.2 (9.55)	54.3 (13.69)	58.9 (13.65)	56.8 (12.35)
Male, n (%)	5 (38.5)	10 (71.4)	3 (21.4)	18 (43.9)
Female, n (%)	8 (61.5)	4 (28.6)	11 (78.6)	23 (56.1)
Ethnicity, n (%)				
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	13 (100)	14 (100)	14 (100)	41 (100)
Unknown	0	0	0	0
Height (cm) Mean (SD)	169.4 (9.87)	176.9 (12.50)	167.5 (9.76)	171.3 (11.33)
Weight (kg) Mean (SD)	82.7 (19.68)	96.7 (27.26)	83.3 (18.03)	87.7 (22.51)
BMI (kg/m ²) Mean (SD)	28.8 (6.49)	30.4 (5.12)	29.7 (6.43)	29.7 (5.92)
NYHA Class (n)				
Class II	11 (84.6)	10 (71.4)	7 (50.0)	28 (68.3)
Class III	2 (15.4)	4 (28.6)	7 (50.0)	13 (31.7)
Background hypertrophic cardiomyopathy therapy, n (%)				
β-Blocking Agents	11 (84.6)	9 (64.3)	11 (78.6)	31 (75.6)
Non-dihydropyridine Calcium Channel Blockers	2 (15.4)	5 (35.7)	2 (14.3)	9 (22.0)

Source: Table 1 in BTDR briefing document

The primary objective of the study was to determine safety and tolerability of aficamten in patients with symptomatic oHCM. Data from Cohort 1 and Cohort 2 showed that the incidence of AEs was similar between treatment arms, there were no AEs that resulted in treatment interruption or discontinuation, and no aficamten-related SAEs (only 1 SAE of back pain was reported in aficamten-treated patients from Cohort 1). None of the subjects in Cohort 1 experienced a reduction in LVEF < 50% during the study. Two subjects in Cohort 2 had an LVEF < 50%; LVEF returned > 50% for both cases after per-protocol dose reduction or study drug discontinuation. No subjects in CY 6021 met the stopping criteria of LVEF < 40%.

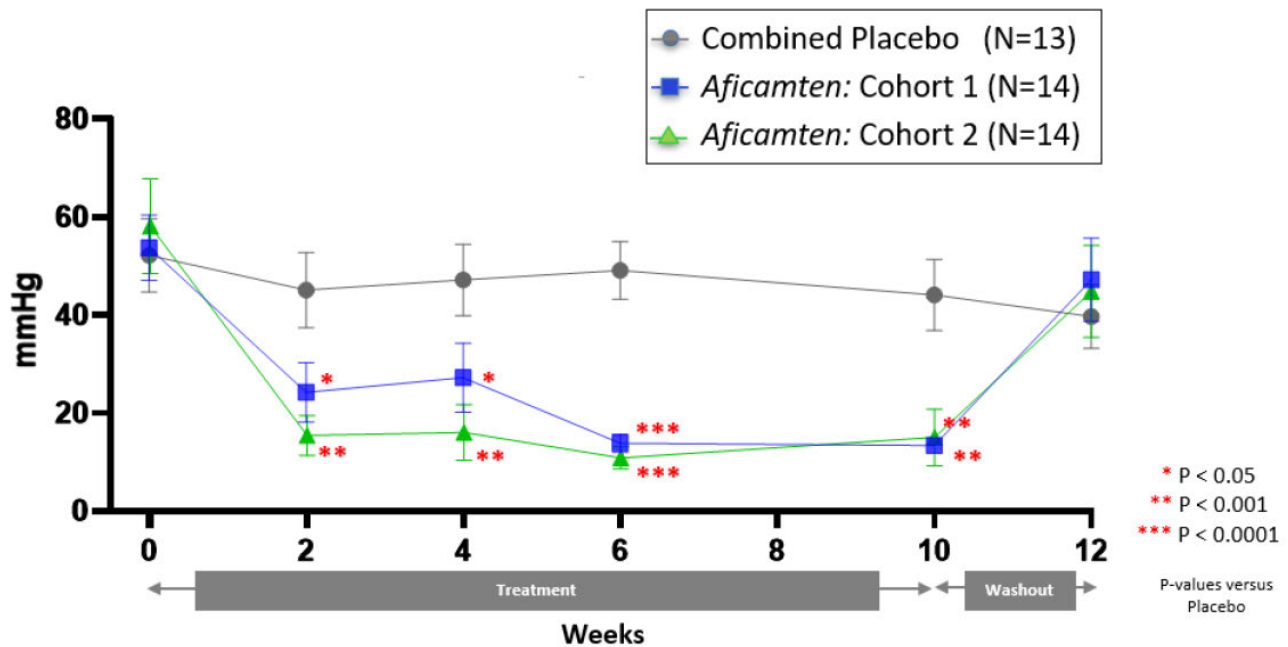
The preliminary efficacy was assessed as secondary and exploratory endpoints from Cohorts 1 and 2 and the results are presented as follows:

Hemodynamic effects:

- Treatment with aficamten resulted in a marked decrease in the mean resting LVOT-G at Week 10 ($\Delta = -40 \pm 27$ mmHg and -43 ± 37 mmHg in Cohorts 1 and 2, respectively) compared with placebo ($\Delta = -10 \pm 24$ mmHg) ($p = 0.009$ for Cohort 1 and $p = 0.0003$ for Cohort 2) (Figure 1)
- A similar treatment effect was seen in provoked (Valsalva) peak LVOT-G at Week 10 ($\Delta = -36 \pm 27$ mmHg and -53 ± 44 mmHg in aficamten-treated subjects in Cohorts 1 and 2, respectively) versus placebo ($\Delta = -10 \pm 21$ mmHg) ($p = 0.01$ for Cohort 1 and $p = 0.008$ for Cohort 2) (Figure 2).
- There was return of resting LVOT-G or peak post-Valsalva LVOT-G in aficamten groups at Week 12 after treatment discontinuation at Week 10 (Figure 1 and Figure 2)
- A higher proportion of subjects achieved a hemodynamic response using both the resting and post-Valsalva LVOT-G into a categorical responder analysis at Week 10 (resting LVOT-G of < 30 mmHg and a post-

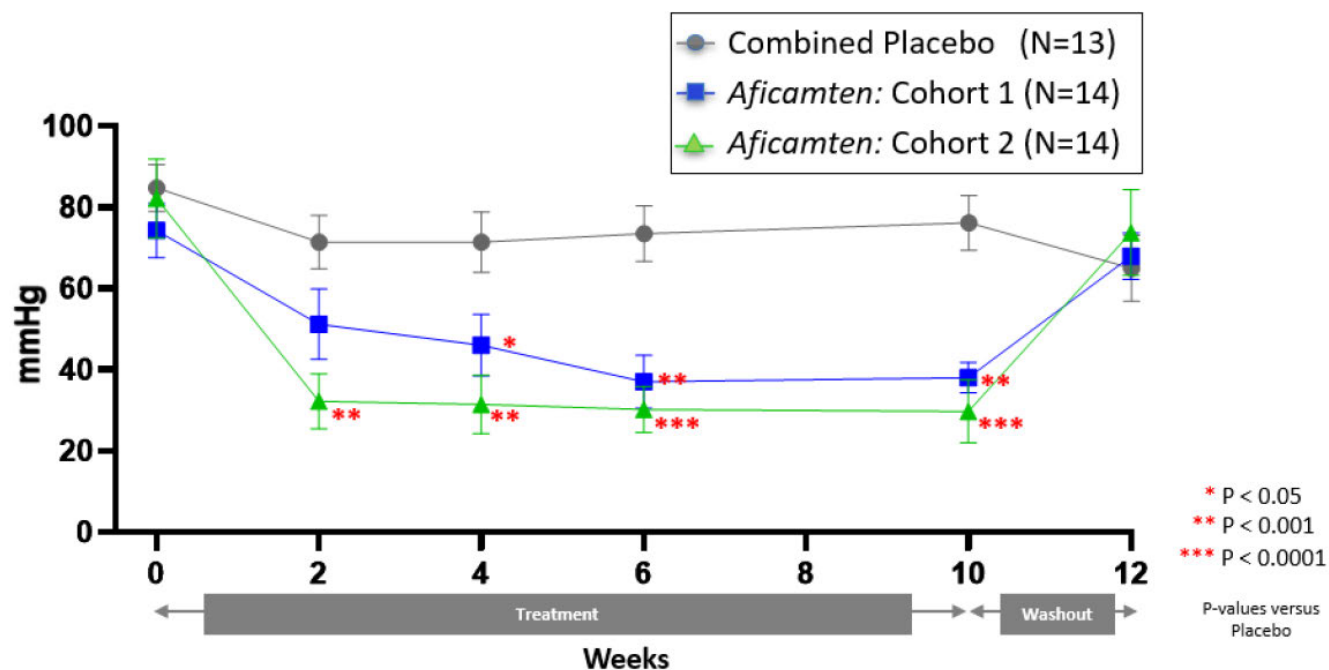
Valsalva LVOT-G < 50 mmHg) in aficamten-treated subjects in both Cohorts (79% and 93%, respectively) compared with placebo (8%) (Figure 3).

Figure 1 Mean Peak Resting LVOT-G (mmHg) Over Time, CY6021, Cohorts 1 and 2



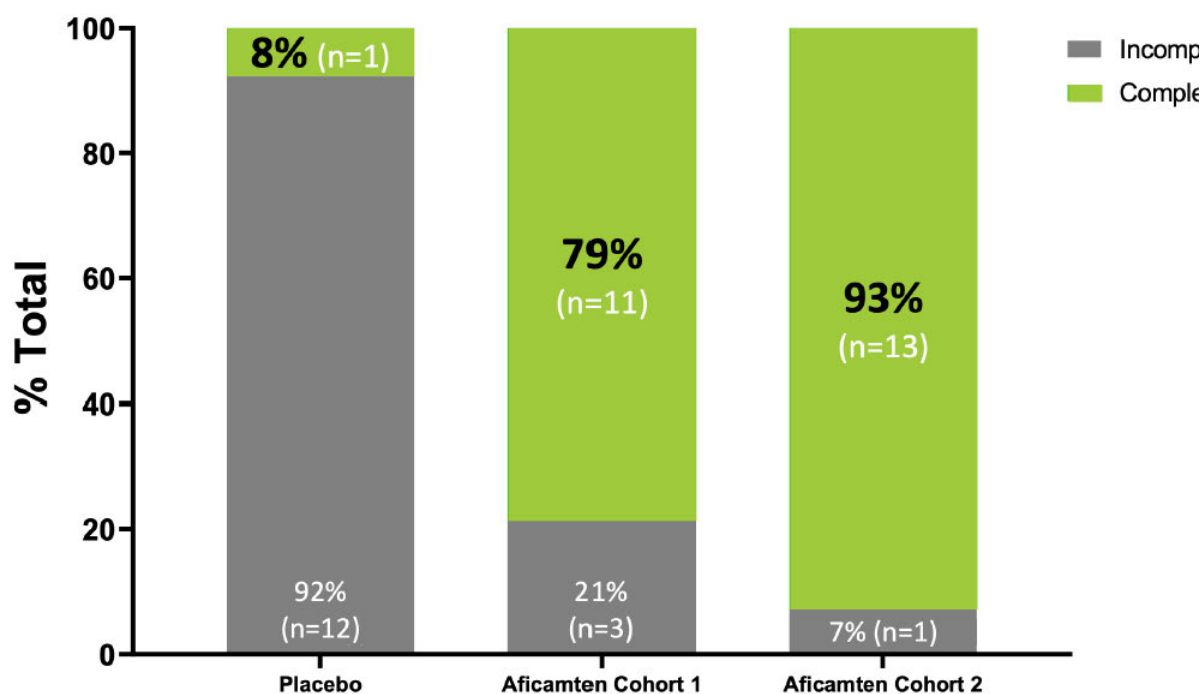
Source: Figure 2 in BTDR briefing document

Figure 2 Mean Peak Post-Valsalva LVOT-G Over Time, CY 6021, Cohorts 1 and 2



Source: Figure 3 in BTDR briefing document

Figure 3 Proportion of Patients Achieving Complete Hemodynamic Response at Week 10, CY 6021, Cohorts 1 and 2



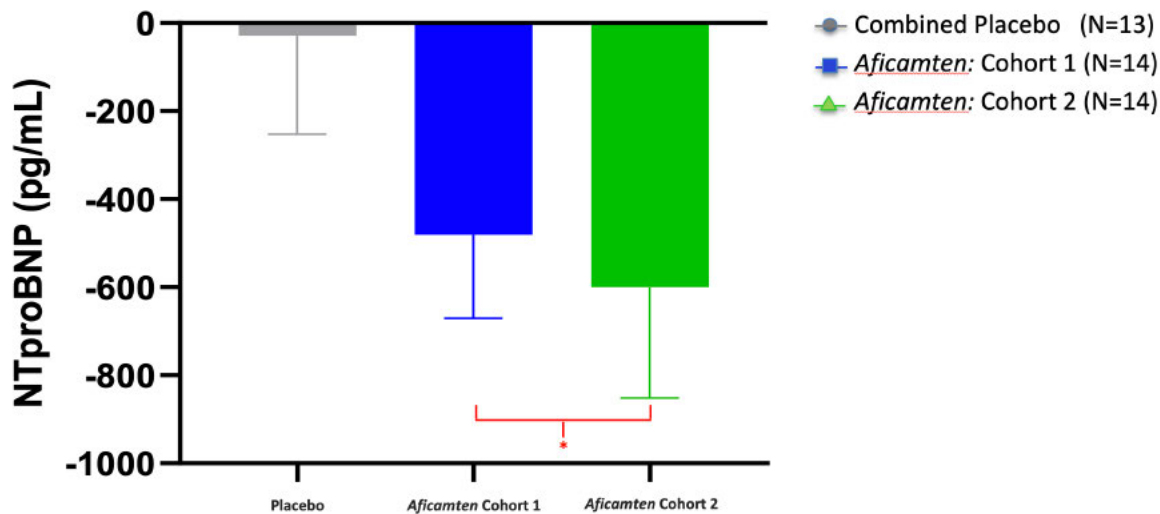
Week 10 Responder = Resting LVOT-G <30 mmHg and post-Valsalva LVOT-G <50 mmHg.

Source: Figure 4 in BTDR briefing document

Key Exploratory/Functional Endpoints

- Mean NT-proBNP was decreased from baseline in aficamten-treated arms of both Cohorts 1 and 2 but not in the placebo treated arm (Figure 4). The proportional change from baseline (i.e., the ratio of NT-proBNP at Week 10 to NT-proBNP at baseline) was noticeably smaller for the aficamten-treated patients (0.49 and 0.25 for Cohort 1 and Cohort 2, respectively) versus the placebo arm (1.00).
- There was a trend showing a higher proportion of aficamten-treated subjects with improvement in NYHA Class ≥ 1 in Cohort 2 (higher doses of aficamten) compared to placebo (64% vs. 31%, $\Delta = 32\%$, $p = 0.08$). A modest effect was observed at the lower doses employed in Cohort 1 compared to placebo (43% vs. 31%, $\Delta = 12\%$, $p > 0.1$) (Figure 5).

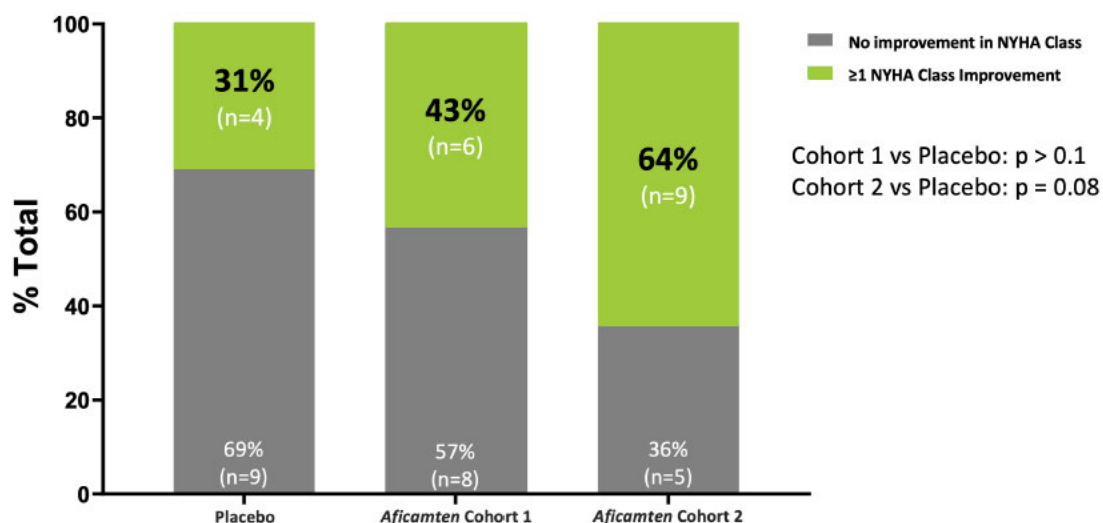
Figure 4 Change from Baseline in NT-proBNP, CY 6021, Cohorts 1 and 2



* $P = 0.003$ for pooled Cohort 1 and 2 versus placebo

Source: Figure 6 in BTDR briefing document

Figure 5 Improvement in NYHA Function Class, CY 6021, Cohorts 1 and 2



Week 10 Responder = Improvement in NYHA Class ≥ 1 .

Source: Figure 7 in BTDR briefing document

b. Summary of Evidence and Additional Relevant Information.

- The observed hemodynamic effects of aficamten (e.g., reduction in LVOT-G) in this double-blind, placebo-controlled Phase 2 study were on top of β -blockers (76% of patients were on β -blockers at baseline). Subgroup analysis indicated that the LVOT-G was reduced in aficamten-treated patients regardless of whether β -blockers were used at baseline. NT-proBNP, a marker of cardiac wall stress, was also decreased by treatment with aficamten.
- The pharmacodynamic effects of aficamten (LVOT-G, LVEF, and NT-proBNP) appeared readily reversible with discontinuation of drug therapy.
- The only functional endpoint explored in this Phase 2 study was NYHA Class. The observed reduction of outflow gradient was associated with a trend for improvement in heart failure functional status by achieving one or more improvement in NYHA class; the impact of aficamten on NYHA Class was more obvious in higher doses group (Cohort 2). The proposed Phase 3 study will allow aficamten dose titration up to 20 mg (all but one subject in Cohort 2 had aficamten dose 20 mg or under at Week 10).
- The majority of aficamten-treated patients with an improvement in NYHA class (13 of 15) also achieved a hemodynamic response (both resting [<30 mmHg] and Valsalva [<50 mmHg] LVOT-G) and nearly all patients had considerable improvements in NT-proBNP.
- Aficamten demonstrated similar hemodynamic effects as Mavacamten, another inhibitor of cardiac myosin, currently under the NDA review and is expected to have some positive effects on functional capacity and symptoms relief.
- This class of drugs demonstrates a concentration-dependent decrease in LVEF. The major safety concern of aficamten is the potential risk of heart failure due to systolic dysfunction resulting from excessive pharmacologic effect. LVEF decreases were expected and reasonable in the Phase 2 data with a median decrease from baseline of 3.5% in Cohort 1 and 9.7% in Cohort 2.
- This class of drugs also has long-half life and metabolites predominating clearance. The terminal $t_{1/2}$ of aficamten was ~ 75 to 85 hours and steady state was achieved by ~ 14 days. CYP2D6 is the major enzyme metabolizing aficamten ($\sim 50\%$ contribution). Preliminary data did not suggest that CYP2D6 poor metabolizers have a different PK profile as compared to that in normal CYP2D6 metabolizers. In contrast, Mavacamten's exposure and clearance are significantly impacted by CYP2C19 genotype and it has a complex PK profile in terms of drug-drug interactions which complicate safe dosing algorithms and dosing instructions. It would be of advantage if aficamten is free of this liability.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

CY 6021 Phase 2 data demonstrated sizeable hemodynamic effects of aficamten on top of β -blockers, which are expected to be translated into some degree of clinical benefits on functional improvements and symptoms relief. The preliminary clinical evidence also suggested a trend for improving functional status as measured by NYHA class. Considering the paucity of approved therapeutic options for oHCM, the use of aficamten as a second-line or add-on therapy may delay or obviate invasive septal reduction therapy.

☐DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

The Division recently reviewed the proposed Phase 3 study and will continue to work with the sponsor and provide advice on the development program.

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

The Council had reviewed the request and agreed with DCN's recommendation to grant Cytokinetic Inc.'s BTDR.

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 10/13/20 /M. Raggio

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/

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NORMAN L STOCKBRIDGE
12/03/2021 09:03:42 AM

IND 138814

MEETING PRELIMINARY COMMENTS

Cytokinetics, Inc.
Attention: Rachel E. Melman, MBS RAC
Senior Director, Regulatory Affairs
280 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Melman:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CK-3773274.

We also refer to your May 27, 2021, correspondence requesting an End-of Phase-2 (EOP2) meeting to obtain FDA guidance and concurrence on the nonclinical program and the design and adequacy of the proposed Phase 3 trial, CY 6031.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, please call me at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Alexis Childers, RAC, CQIA
Sr. Regulatory Health Project Manager
Cardiology and Nephrology
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: August 12, 2021, 12:00-1:00 pm EDT
Meeting Location: Teleconference

Application Number: 138814
Product Name: CK-3773274

Indication: treatment of obstructive hypertrophic cardiomyopathy (oHCM), to improve (b) (4)

Sponsor Name: Cytokinetics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

**Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)*
Ellis F. Unger, MD Director

**OCHEN, Division of Cardiology and Nephrology*
Norman Stockbridge, MD, PhD Director
Aliza Thompson, MD Deputy Director
Mary Ross Southworth, PharmD Deputy Safety Director
Preston Dunnmon, MD, MBA Clinical Team Leader
Tzu-Yun McDowell, PhD Clinical Reviewer

**OCHEN, Division of Pharmacology/Toxicology*
Gowra Jagadeesh, PhD Pharmacologist
Xuan Chi, PhD Pharmacology Team Leader

**Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology*
Edward Fromm, RPh, RAC Chief, Project Management Staff
Alexis Childers, RAC, CQIA Sr. Regulatory Health Project Manager

**Office of Clinical Pharmacology, Division of Clinical Pharmacology I*
Manoj Khurana, PhD Clinical Pharmacology Team Leader
Xiaolei Pan, PhD Clinical Pharmacology Reviewer

**Office of Biometrics, Division of Biometrics I*
Jialu Zhang, PhD Statistical Team Leader
Jennifer Clark, PhD Statistician

SPONSOR ATTENDEES**Cytokinetics**

Robert I. Blum	President and Chief Executive Officer
Bonnie Charpentier, PhD	Senior Vice President, Regulatory Affairs and Compliance
Polina German, PharmD	Head of Clinical Pharmacology
Stephen B. Heitner, MD, FACC, FASE	Senior Medical Director, Clinical Research, Cardiovascular
Victoria Herbert, MS	Senior Manager, Regulatory Affairs
Stuart Kupfer, MD	Senior Vice President, Chief Medical Officer
Fady Malik, MD, PhD, FACC, FHFA	Executive Vice President, Research and Development
Rachel Melman, MBS RAC	Senior Director, Regulatory Affairs
Lixin Meng, PhD	Senior Director, Biometrics
Bradley P. Morgan, PhD	Senior Vice President, Research and Nonclinical Development
Sharon Paige, MD, PhD	Associate Medical Director, Clinical Research, Cardiovascular
Michael Pugsley, PhD, FBPhS, DSP	Director, Toxicology
Laura Robertson, MD	Director, Clinical Research, Cardiovascular
Qi Wohltman, ME	Director, Biostatistics

Consultants

Fran Brown, PhD	Senior Vice President, Drug Development Science, Certara Inc.
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Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for August 12, 2021, from 12:00-1:00 pm EDT between Cytokinetics Inc. and the Division of Cardiology and Nephrology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions

based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

CK-3773274 is a small molecule, allosteric inhibitor of cardiac myosin. Cytokinetics is developing CK-3773274 for once daily chronic oral administration for the treatment of obstructive hypertrophic cardiomyopathy (oHCM). Cytokinetics met with the Division in June 2018 to discuss the initial IND opening study CY 6011 and subsequently submitted the IND in October 2018. The study completed in May 2019. In April 2019, Cytokinetics requested a meeting to discuss a phase 2 study, CY 6021, in patients with symptomatic oHCM. After receiving the Division's preliminary responses in June 2019, Cytokinetics requested meeting cancellation. A meeting was conducted in June 2021 to discuss data from the first cohort for study CY 6021 and major elements of a Phase 3 trial, CY 6031.

CY 6031 is a double-blind, placebo-controlled trial to evaluate the effect of CK3773274 on exercise capacity, health status, and NYHA functional class. Approximately 270 subjects will be randomized to CK3773274 or placebo. Subjects randomized to CK3773274 will receive escalating doses (up to 4 doses total) every 2 weeks through Week 6 using echocardiography to guide dose titration. Patients randomized to placebo will undergo dose titration in a similar fashion to maintain blinding. The primary endpoint is change in peak oxygen uptake (pVO₂) following 24 weeks of treatment. Cytokinetics plans to initiate the trial in 4Q 2021. This meeting was requested to discuss the nonclinical and clinical pharmacology development programs to date, and to gain concurrence on the design of CY 6031.

2.0 DISCUSSION

2.1. Nonclinical

1. Does FDA agree that the completed and planned characterization of the metabolites CK-3834282 and CK-3834283 is adequate to support a potential future NDA submission?

FDA response: The completed and planned characterization of metabolites CK-3834282 and CK-3834283 outlined in your meeting briefing document seems to be adequate to support a potential future NDA submission. The final determination will be made during the NDA review. To help the final determination, please submit study reports to support the lack of pharmacodynamic effects of the metabolites on the drug target and the completed two-week tolerability study with the metabolites in rats.

2. Does FDA agree that the nonclinical studies completed to date are sufficient to support conduct of the proposed Phase 3 safety and efficacy trial, CY 6031?

FDA response: Yes, we agree.

3. Does FDA agree that the nonclinical program (completed, ongoing, and planned studies) is sufficient to support a potential future NDA submission (see Section 5 and Appendix 1)?

FDA response: Yes, we agree.

2.2. Clinical/Statistical

4. Does FDA agree that the clinical pharmacology program (completed, ongoing, and planned studies) is adequate to support review of a potential future FDA submission (see Section 6.1)?

FDA response: While your clinical pharmacology program seems reasonable to support a future NDA submission, we have the following comment for you to address:

In vitro studies identified that CK-3773274 is mainly metabolized by CYP2D6, with a minor contribution from several other CYP isoforms (2C9, 2C19 and 3A4). Although CYP2D6 poor metabolizers did not appear to have a clinically meaningful difference in exposure as compared with non-poor metabolizers in Study 6011, potential risks for drug interactions between CK-3773274 and CYP2D6 inhibitors cannot be fully excluded based on these results. We recommend conducting a clinical drug interaction study between CK-3773274 and CYP2D6 inhibitors to assess the drug interaction potential between CK-3773274 and CYP2D6 inhibitors. Please refer to FDA-Guidance for Industry - clinical drug interaction studies for cytochrome P450 enzyme- and transporter-mediated drug interactions for details found at: <https://www.fda.gov/media/134581/download>.

5. Does FDA agree with the overall design of the proposed Phase 3 trial CY 6031, specifically the proposed doses and dose titration strategy (see Section 6.3 and Section 6.3.1.1)?

FDA response: We agree with your proposed dose titration strategy. However, with respect to your proposal for handling missing data, we do not agree that a

(b) (4)

A multiple imputation (MI) analysis similar

to what you describe for your sensitivity analysis is more in line with this estimand. We recommend that you describe any potential intercurrent events (e.g., death, treatment discontinuation) and your planned approach to address these intercurrent events. We do note that if you maintain a minimal amount of missing data in your study, then there will be little difference among these analyses.

Additionally, we would like you to include a 2-way tipping point analysis as an additional sensitivity analysis to explore the robustness of your analysis results. We would like to see departures from the estimated treatment difference evaluated by varying imputed data in both treatment arms simultaneously. Please include interpretations for the varying scenarios and how likely they would be seen in a real-world setting. Your tipping point analyses should address all plausible scenarios, including those in which the outcomes for patients missing data are worse among patients randomized to treatment than among patients randomized to control. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect.

We recommend restricting the use of strong and moderate CYP2D6 inhibitors in the proposed Phase 3 trial before this drug interaction risk has been fully evaluated.

6. In the Phase 3 trial CY 6031, secondary endpoints of post-Valsalva LVOT gradient, NYHA Functional Classification, and Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score will be evaluated at both Week 12 and Week 24 (end of study). If these Week 12 and Week 24 assessments are clinically meaningful and statistically significant, does FDA agree that these data could be included in Section 14 (Clinical Studies) of the potential future prescribing information (see Section 6.3.1.3)?

FDA response: Of these, LVOT is not a clinical endpoint and can reasonably be assessed outside the alpha conserving plan. Its results may be described in section 12. Others would be described in section 14—and may lead to additional claims.

2.3. Regulatory

7. Orphan drug designation was granted for CK3773274 for the treatment of symptomatic HCM. Does FDA agree submission of an initial Pediatric Study Plan (iPSP) for CK-3773274 is not required (see Section 7.1)?

FDA response: Yes, we agree.

Additional Requests from the Agency

1. Prior to initiation of your phase 3 trial, please submit to the IND an encrypted SAS dataset of the randomization list including the randomization number, treatment arm, and stratification factors (if any). Please include an unencrypted define file describing the randomization list variables. Submit the encryption key with the NDA and reference the IND submission date and serial number.
2. The vital status of all subjects should be known at the end of phase 3 trial. Therefore, we recommend that you conduct this trial in jurisdictions where determination of vital status from public records is permitted by local regulations in the event that any subjects are lost to follow-up.
3. One study like 6031 successful with $p \approx 0.05$ is not a basis for approval. Plan for two such studies, a single study with $p < 0.01$, or consider endpoints with greater clinical significance—like death or hospitalization.

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.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

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.³

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁴ 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁵

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized

⁵ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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 Resources⁶ and the CDER/CBER Position on Use of SI Units for Lab Tests website.⁷

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁷ <https://www.fda.gov/media/109533/download>

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection*

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

of Race and Ethnicity Data in Clinical Trials for more information.

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

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/

ALEXIS T CHILDERS
08/03/2021 11:00:33 AM