CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217564Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131038

MEETING MINUTES

HUTCHMED Limited
Attention: John M. Adams, Pharm.D., RAC
Senior Director, Regulatory Affairs
HUTCHMED International Corporation
25A Vreeland Road, Suite 304
Florham Park, NJ 07932

Dear Dr. Adams:

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

We also refer to the video conference between representatives of your firm and FDA on October 20, 2022. The purpose of the meeting was to discuss the upcoming submission of a 505(b)(1) NDA for fruquintinib.

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 me at 301-837-7646 or email me at Craig.Long@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Craig Long
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 20, 2022; 2:00PM-3:00PM, EST
Meeting Location:	Video conference
Application Number:	IND 131038
Product Name:	fruquintinib
Indication:	Treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy
Sponsor Name:	HUTCHMED Limited
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	'Lola Fashoyin-Aje, M.D., M.P.H.
Meeting Recorder:	Craig Long, Pharm.D.

FDA ATTENDEES

'Lola Fashoyin-Aje, M.D., M.P.H., Deputy Division Director, OOD/DO3
Sandra Casak, M.D., Clinical Team Leader, OOD/DO3
Shruti Gandhy, M.D., Ph.D., Clinical Reviewer, OOD/DO3
Matthew Thompson, Ph.D., M.P.H., Nonclinical Team Leader, OOD/DHOT
Jason Moore, Pharm.D., Clinical Pharmacology Team Leader, OCP/DCPI
Joyce Cheng, Ph.D., Statistical Team Leader, OB/DBV
Sirisha Mushti, Ph.D., M.Sc., Statistical Reviewer, OB/DBV
Craig Long, Pharm.D., Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES

Marek Kania, M.D., MBA, Executive VP, HUTCHMED International Corporation
William Schelman, M.D., Ph.D., VP, HUTCHMED International Corporation
Shivani Nanda, M.S., Executive Director, HUTCHMED International Corporation
Tony Yang, Ph.D., Director, HUTCHMED International Corporation
Caly Chien, Ph.D., RPh, Executive Director, HUTCHMED International Corporation
Robyn Rantuccio, Pharm.D., VP, HUTCHMED International Corporation
John Adams, Pharm.D., RAC, Senior Director, HUTCHMED International Corporation

Mark Woods, M.S., Director, HUTCHMED Europe BV

BACKGROUND

Regulatory

On August 25, 2016, Hutchison MediPharma Ltd. submitted an original Investigational New Drug Application (IND) containing Protocol 2015-013- 00US1, entitled “A Multi-Center, Open-Label, Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics of Fruquintinib in Advanced Solid Tumors in USA,” for fruquintinib (HMPL-013) in advanced solid tumors. The IND went into effect on September 23, 2016.

On December 12, 2019, Hutchison MediPharma Ltd. submitted a Type B, End-of-Phase 2, meeting request to seek guidance on the proposed global study rationale and design, the proposed indication for the treatment of patients with metastatic colorectal cancer, a pediatric study waiver request, the clinical pharmacology development plan, the potential for accelerated approval, and the clinical safety database and toxicology program conducted under China Good Laboratory Practices (GLP) to support a New Drug Application (NDA) submission.

Fast track designation for fruquintinib was granted on June 15, 2020.

A PSP waiver in all pediatric indications was approved on September 18, 2020.

On January 7, 2022, FDA received a correspondence notifying the Agency that the corporate name has been changed from Hutchison MediPharma Ltd. to HUTCHMED Limited (Hutchmed).

On January 21, 2022, Hutchmed submitted a Type C meeting request to gain alignment with the Agency on the proposed format and content of the NDA. FDA issued Written responses on March 29, 2022.

On August 22, 2022, Hutchmed submitted a Type B meeting request to discuss with the Agency key agreements to enable the submission of a complete NDA . FDA granted this meeting request on August 25, 2022.

FDA sent Preliminary Comments to Hutchmed on October 14, 2022.

Clinical

Fruquintinib is an oral tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors -1, -2, and -3 and is approved in China for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF

therapy, or, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy; the FRESCO trial (NCT02314819) was the basis for approval. This trial was a multicenter, randomized, double-blind, placebo-controlled study. Patients were stratified based on prior anti-VEGF therapy and KRAS status and randomized to receive fruquintinib or placebo in a 2:1 ratio. The primary endpoint was overall survival (OS). A total of 416 eligible patients were randomized in 28 sites in China to receive fruquintinib (n = 278) or placebo (n = 138) and were included in the intention to-treat (ITT) population. Median OS was 9.30 months [95% confidence interval (CI), 8.18,10.45] in the fruquintinib group and 6.57 months (95%CI, 5.88, 8.11) in the placebo group [hazard ratio (HR) 0.65, 95% CI 0.51, 0.83: log-rank test P < .001]. Median progression-free survival (PFS) was 3.71 months (95% CI 3.65, 4.63) vs 1.84 months (95% CI 1.81, 1.84) with placebo (HR 0.26, 95% CI 0.21, 0.34; P < .001). Adverse events (AEs) were reported in 99% and 88% patients in the fruquintinib and placebo arms, respectively. The incidence of serious adverse events (SAEs) was 15.5% and 6% in the fruquintinib and placebo arms, respectively. The most frequently reported AEs deemed by the investigators to be related to investigational treatment were hypertension (55% vs 15%), palmar-plantar erythrodysesthesia syndrome (49% vs 3%), proteinuria (42% vs 25%), dysphonia (36% vs 1.5%), and thyroid stimulating hormone (TSH) increased (25% vs 2%). Grade 3-4 AEs were reported in 45% and 7% patients in the fruquintinib and placebo arms, respectively. Fatal AEs were reported in 3.2% and 1.5% in the fruquintinib and placebo arms, respectively.

To support approval in the U.S., Hutchmed completed Study 2019-013-GLOB1 (FRESCO-2, NCT04322539), a multicenter, international, randomized, double-blind, placebo-controlled trial in patients with mCRC with disease progression after fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF therapy, anti-EGFR therapy (if RAS wild-type), and TAS-102 and/or regorafenib.
691 patients were randomized 2:1 to receive:

- Fruquintinib 5 mg PO daily plus best supportive care for 3 weeks on, 1 week off (461 patients), OR

- Placebo 5 mg PO daily plus best supportive care 3 weeks on, 1 week of (230 patients).

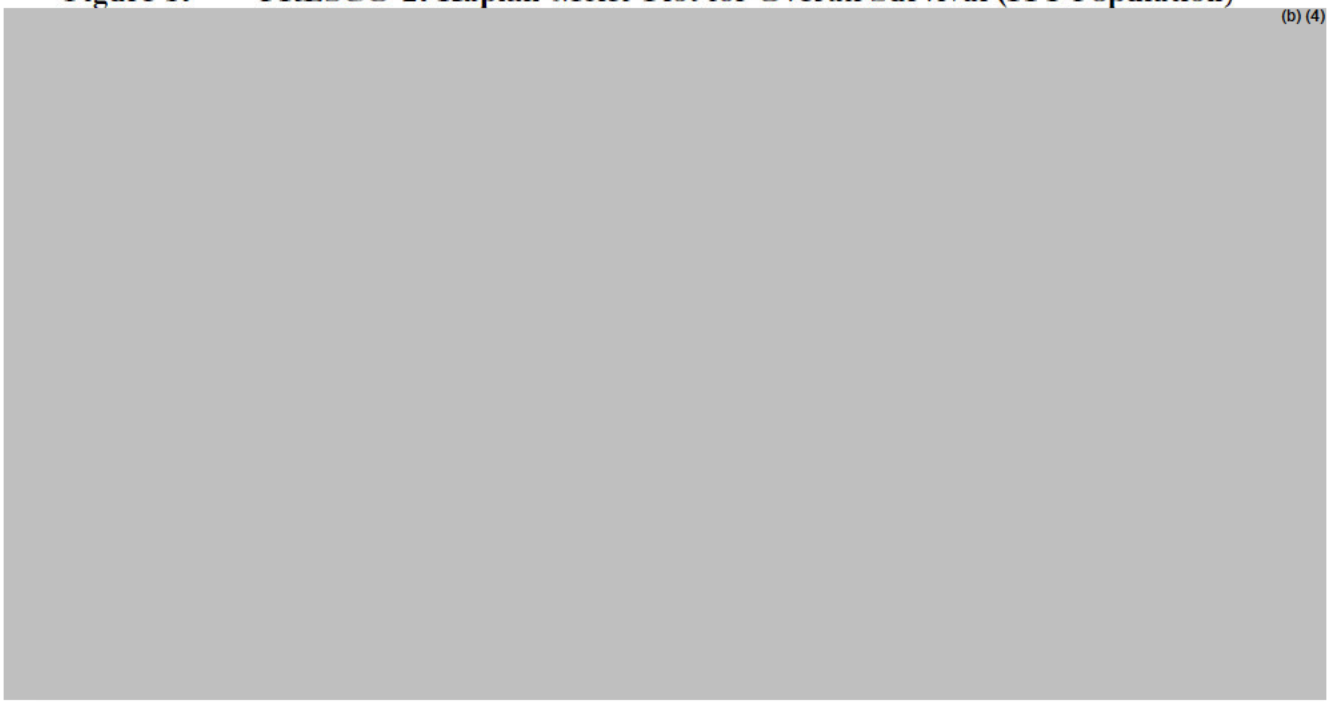
Randomization was stratified by:

- Prior therapy with TAS-102 vs regorafenib vs both
- RAS status (wild type vs mutant)
- Duration of metastatic disease (≤18 months vs >18 months)

Tumor assessments were conducted every 8 weeks until progression of disease (PD), death, intolerable toxicity, or withdrawal of consent. The primary efficacy endpoint was OS in the ITT population. Main secondary endpoints were PFS and overall response rate (ORR).
The final analysis was conducted when 490 (71%) OS events had occurred (data cut off

date of June 24, 2022). The absolute difference in median OS was 2.6 months, with a median OS in the fruquintinib group of 7.4 months (95% CI: 6.7, 8.2) and the median OS in the placebo group of 4.8 months (95% CI:4.0, 5.8) with a HR of 0.662 (95% CI: 0.55, 0.8; p < .001). Median PFS in the fruquintinib group was 3.7 months (95% CI: 3.5, 3.8) compared to 1.8 months (95% CI: 1.8, 1.9) in the placebo group. ORR was 1.5% in the fruquintinib group (95% CI: 0.4 ,2.7) and 0% in the placebo group.

Figure 1: FRESCO-2: Kaplan-Meier Plot for Overall Survival (ITT Population)



Abbreviations: BSC=best supportive care; CI=confidence interval; CSR=clinical study report; fruq=fruquintinib; HR=hazard ratio; ITT=intent-to-treat; mOS=median overall survival; no.=number; plc=placebo.
Source: Study 2019-013-GLOB1 (FRESCO-2) Draft CSR, Figure 14.2.1.1.3

Source: Meeting package, page 30.

Grade ≥ 3 AEs were observed in 62.7% of patients treated with fruquintinib vs 50.4% in those treated with placebo; those occurring in ≥ 5% in patients treated with fruquintinib were hypertension (13.6% [fruquintinib] vs 0.9% [placebo]), asthenia (7.7% [fruquintinib] vs 3.9% [placebo]), and palmar-plantar erythrodysesthesia syndrome (6.4% [fruquintinib] vs 0% [placebo]).

Hutchmed proposes a rolling submission. The non-clinical components will be submitted no later than December 2022, followed by the clinical, quality, and administrative components no later than the end of March 2023.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical

1. *Does the Agency agree that the clinically meaningful and statistically significant improvement in OS observed in the pivotal FRESCO-2 Study warrants submission and review of the NDA?*

   FDA Response: FDA does not object to the submission of an NDA for fruquintinib based on the results of the FRESCO-2 trial for the treatment of patients with refractory mCRC. FDA notes that the indication will be a review issue.

   Prior to submitting the application, ensure that every clinical site will permit a site inspection if deemed necessary by FDA. If inspectors are not permitted at a site (or if inspections are delayed) FDA may issue a complete response letter to the application.

   Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

   Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

2. *Does the Agency agree that the efficacy and safety data from the Multi-Regional Clinical Trial FRESCO-2 study and the FRESCO Study constitute the basis for approval of fruquintinib for the proposed mCRC indication as discussed in prior meetings with the FDA?*

   FDA Response: FDA does not object to the submission of an application based on the results of the FRESCO and FRESCO-2 trials. Adequacy of the studies' results to support the approval of fruquintinib for the treatment of patients with refractory mCRC will be a review issue.

   Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

   Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

3. *Does the Agency agree that the efficacy and safety results from the FRESCO-2 and FRESCO Studies warrant a priority review of the planned NDA?*

FDA Response: It is premature to answer this question. Review timelines are determined upon filing of an application.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

4. *Does the Agency agree with the proposed schedule and plan for submitting an NDA on a rolling basis?*

FDA Response: FDA does not object to the proposed schedule for rolling submission.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and will submit a "Request for Submission of Portions of an Application" to IND 131038 no later than 11 November 2022. Nonclinical components will be submitted no later than December 2022, followed by the clinical, quality, and related administrative components no later than the end of March 2023.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

5. *Does the Agency agree with the current proposal for the clinical electronic submission package for the FRESCO Study to address the written response received from the Type C meeting (dated 29 March 2022)?*

FDA Response: The proposal to submit two separate data packages is acceptable; however, at the time of the application review FDA reviewers may request that Hutchmed submits any additional information required to perform the efficacy and safety analysis.

In addition to the submission of SAS programs used to produce the datasets, submit the executable SAS programs used to generate the efficacy results corresponding to the primary and key secondary endpoints.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

6. *Does the Agency agree that a risk evaluation and mitigation strategy (REMS) is not needed and that a waiver is warranted based on the safety and efficacy data from the two pivotal FRESCO-2 and FRESCO Studies and the known safety data for fruquintinib?*

FDA Response: Based on a preliminary assessment of the topline safety data, FDA agrees that a REMS would be unlikely; final determination of the need for a REMS will be a review issue.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

7. *Does the Agency agree with the Sponsor's proposal regarding the scope, content, and timing of the 120-Day safety update?*

FDA Response: FDA agrees.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

8. *Does the Agency agree with the refinements the Sponsor made to the Integrated Summary of Safety (ISS) Statistical Analysis Plan to support the summary of clinical safety (SCS) and label?*

FDA Response: FDA does not object to the proposed plan for the ISS and SCS.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment and has no further questions at this time.

Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

ADDITIONAL COMMENTS

Clinical

9. As per 21 CFR 314.50(d)(5)(v), an integrated analysis of efficacy (ISE) is required a part of an NDA submission. Refer to FDA's Guidance "*Integrated Summary of Effectiveness Guidance for Industry*": available at https://www.fda.gov/media/72335/download.

   Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's comment.

   The Sponsor's approach for the ISE was detailed in the context of the proposed plan for the summary of clinical efficacy (SCE) in the Type C meeting information package (IND 131038; SN0157). Namely, the two pivotal studies, FRESCO-2, and FRESCO, will form the basis of the SCE with additional supporting data from other studies in mCRC. The SCE will include key efficacy tables and figures from FRESCO-2 and FRESCO with supporting studies in the summary text (Module 2.7.3) and other relevant tables and listings in the appendix (Module 2.7.3.6).

   Since the Sponsor does not plan to pool efficacy data for the FRESCO-2 and FRESCO studies due to the differences in treatment paradigms in the studies, no Statistical Analysis Plan (SAP) for an ISE will be developed. The requirement for the ISE will be met by including additional tables, figures, and listings, supplementary to those presented in the SCE, in Module 5.3.5.3 of the NDA.

   Discussion During the October 20, 2022, Teleconference: FDA acknowledged Hutchmed's response; there was no further discussion of this item during the meeting.

Clinical Pharmacology

10. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "*Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*". Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

11. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who

required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

12. What are the exposure-response relationships for efficacy, safety, and biomarkers?

13. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

14. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

15. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

16. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

    - Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption, or discontinuation; the reasons for dosage modifications in the datasets.

17. Submit the following for the population pharmacokinetic analysis reports:

    - Standard model diagnostic plots

    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line, and the population prediction line

    - Model parameter names and units in tables

- Summary of the report describing the clinical application of modeling results

18. Submit the following information and data to support the population pharmacokinetic analysis:

    - SAS transport files (*.xpt) for all datasets used for model development and validation

    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

    - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

19. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

20. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Hutchmed response received via email on October 18, 2022: The Sponsor acknowledges the FDA's additional comments and guidance. The Sponsor intends to follow this guidance.

- Regarding FDA Comment #15, the Sponsor plans to provide an update regarding the clinical pharmacology content of the application during the pre-NDA meeting. Reporting for Study 2021-013-00US3, a Phase 1 study to evaluate the effect of fruquintinib on the pharmacokinetics (PK) of dabigatran etexilate (a P-gp

substrate) and rosuvastatin (a BCRP substrate) in healthy subjects, will be discussed.

- Regarding FDA Comment #16, the Sponsor will provide complete datasets in CDISC standard for clinical pharmacology studies that started after 17 December 2016 only as noted in the Type C meeting information package (IND 131038; SN0157). For legacy studies that started before 17 December 2016, the datasets for drug concentration-time data and derived PK parameters will be provided as SAS transport files (*.xpt), the subject level analysis dataset, trial summary, and a description of each data item will be provided as a dataset specification file (*.pdf). Clinical data will be provided as raw datasets in SAS files (*.sas7bdat).

Discussion During the October 20, 2022, Teleconference: The Sponsor provided an update on Study 2021-013-00US3. The Sponsor has been experiencing unexpected delays in delivery of PK data due to issues related to the analysis of dabigratran and rosuvastin at (b) (4) Sponsor expects to resolve the issues in mid-November 2022. Instead of providing the final report in the NDA, sponsor is proposing to provide a preliminary PK report that includes topline results in the original NDA submission; the Sponsor expects to submit a final study report in May/June 2023. The Sponsor will provide this report as part of the Day 120 safety update. FDA stated that the proposal appears acceptable provided the topline results are included in the original NDA submission as proposed. FDA emphasized that the application will be considered incomplete without the report containing the proposed topline results. Sponsor acknowledged.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that it is unlikely that a REMS, or other risk management program would be necessary, but a final determination will be made during the review of the NDA.

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

In addition, we note that a CMC pre-submission meeting is planned for November 1,

2022. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

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

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an

iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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 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.

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

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 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in*

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

Applications Submitted to CBER and CDER Questions and Answers[6]*.* 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 information.

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

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Hutchmed provided meeting responses in a document, entitled “Response to FDA Pre-NDA Meeting Preliminary Comments” and a slide deck, entitled “IND 131038 Pre-NDA meeting Sponsor slides”, received via email on October 18, 2022, for the October 20, 2022, meeting.

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[7] https://www.fda.gov/media/85061/download

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/s/

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IND 131038

MEETING MINUTES

Hutchison MediPharma Ltd.
Attention: Deborah Lynch
Senior Director, Regulatory Affairs
Hutchison MediPharma International Inc., Authorized U.S. Agent
25A Vreeland Road, Suite 304
Florham Park, NJ 07932

Dear Ms. Lynch:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fruquintinib (HMPL-013).

We also refer to the meeting between representatives of your firm and the FDA on February 12, 2020. The purpose of the meeting was to discuss the continued development of fruquintinib. Specifically, the proposed study rationale and design, clinical pharmacology development plan, and clinical safety database and toxicology program to support an NDA submission.

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

If you have any questions, call me at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Autumn Zack-Taylor, M.S.
Regulatory Health Project Manager
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	February 12, 2020; 12:00PM-1:00PM EST
Meeting Location:	White Oak Building 22, Conference Room: 1417 Silver Spring, MD 20903
Application Number:	IND 131038
Product Name:	Fruquintinib (HMPL-013)
Indication:	For the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy.
Sponsor/Applicant Name:	Hutchison MediPharma Ltd.
Meeting Chair:	Steven Lemery, M.D., M.H.S.
Meeting Recorder:	Autumn Zack-Taylor, M.S.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S.	Director (Acting), OOD/DO3
Martha Donoghue, M.D.	Clinical Team Leader, OOD/DO3
Sandra Casak, M.D.	Clinical Reviewer, OOD/DO3
Lisa Rodriquez, Ph.D.	Statistical Team Leader, OB/DBV
Mengdie Yuan, Ph.D.	Statistical Reviewer, OB/DBV
Jeanne Fourie Zirkelbach, Ph.D.	Clinical Pharmacology Team Leader, OCP/DCPV
Hisham Qosa, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPV
Miao Zhao, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPV
Matthew Thompson, Ph.D.	Nonclinical Team Leader, OOD/DHOT
Dubravka Kufrin, Ph.D.	Nonclinical Reviewer, OOD/DHOT
Autumn Zack-Taylor, M.S.	Regulatory Health Project Manager, ORO/DO3

SPONSOR ATTENDEES

Marek Kania, M.D., M.B.A.	Senior Vice President, Chief Medical Officer
William Schelman, M.D., Ph.D.	Vice President, Clinical Development
Shivani Nanda	Head of Biostatistics and Data Management
Deborah Lynch	Senior Director, Regulatory Affairs
Caly Chien	Executive Director, Clinical Pharmacology

BACKGROUND

Regulatory

On August 25, 2016, Hutchison MediPharma Ltd. (Hutchison MediPharma) submitted an original Investigational New Drug Application (IND) containing Protocol 2015-013-00US1, entitled "A Multi-Center, Open-Label, Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics of Fruquintinib in Advanced Solid Tumors in USA," for fruquintinib (HMPL-013) in advanced solid tumors. The IND went into effect on September 23, 2016.

On December 12, 2019, Hutchison MediPharma submitted a Type B, End-of-Phase 2, meeting request to seek guidance on the proposed global study rationale and design, the proposed indication for the treatment of patients with metastatic colorectal cancer, a pediatric study waiver request, the clinical pharmacology development plan, the potential for accelerated approval, and the clinical safety database and toxicology program conducted under China GLP to support an New Drug Application (NDA) submission.

Chemistry, Manufacturing and Controls

Fruquintinib drug product is available as 1 mg and 5 mg immediate release oral capsules.

Nonclinical

Hutchison MediPharma states that fruquintinib is a small molecule inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3 and shows anti-tumor activity in various mouse models of cancer. To support an NDA submission, Hutchison MediPharma conducted a 26-week toxicity study in rats, a 39-week toxicity study in dogs, embryo-fetal reproductive toxicity studies in rats, and genotoxicity studies. Based on positive results in embryo-fetal toxicity studies, Hutchison MediPharma states that additional embryo-fetal toxicity studies may not be necessary. Since the general toxicology studies were conducted in compliance with China Good Laboratory Practice (GLP) regulations, Hutchison MediPharma will also conduct a 13-week toxicity study in rats under U.S. GLP regulations as a bridging study.

Clinical Pharmacology

Single-dose and multiple-dose pharmacokinetics (PK) of fruquintinib have been characterized in patient populations in China and the U.S. and single-dose PK has been evaluated in healthy men from China. The exposure of fruquintinib increased proportionally over the single dose range tested from 1 mg to 6 mg in patients with cancer from China. Fruquintinib was rapidly absorbed with mean T_{max} ranging from 1.5 to 4.7 hrs. High fat, high calorie meal delayed T_{max} of fruquintinib by 2.6 hours with a

slight decrease in fruquintinib C_{max} by 17% and no observed effect on $AUC_{0-\infty}$. Mean $T_{1/2}$ ranging from 35.2 to 48.5 hrs was observed for fruquintinib. Following continuous dosing, plasma fruquintinib concentration reached steady state by Day 14 accumulating 3- to 4-fold at steady state compared to Day 1. Preliminary PK results from the U.S. patient population that received fruquintinib at 3 mg and 5 mg QD 3 weeks on/1 week off suggested that there were no meaningful differences in fruquintinib exposure between patients in China and patients in the U.S. The results of a mass balance study showed that a small amount of unchanged fruquintinib was detected in urine (0.5%) and feces (5.34%). In vitro data indicated that fruquintinib is metabolized predominantly by CYP3A, with minor contributions from CYP2C8, CYP2C9, and CYP2C19. M11 (N-desmethylation product) is a major pharmacologically active metabolite with potency approximately 2-10 times lower than that of fruquintinib. At steady-state, the metabolite-to-parent ratio of M11 is 0.41. No reversible or time-dependent inhibition of CYP enzymes were observed for fruquintinib and its metabolites; however, fruquintinib is a P-gp and BCRP transporter inhibitor.

Clinical

Fruquintinib is being developed for a number of different cancer indications, including advanced non-small cell lung cancer (NSCLC), gastric cancer, and metastatic colorectal cancer (mCRC). All clinical studies of fruquintinib except for Study 2015-013-00US1 were conducted in China. Fruquintinib is approved in China for the treatment of patients with mCRC who had been previously treated with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, or, if RAS wild-type, ananti-EGFR therapy. This approval was supported by the results of Study 2013-013-00CH1 (FRESCO), a randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in patients with advanced CRC with disease progression after second-line chemotherapy (Li 2018). Eligible patients were aged 18 to 75 years, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; left ventricular ejection fraction of 50% or greater; measurable disease by RECIST 1.1 and had adequate bone marrow, liver, and renal function. Prior treatment with bevacizumab and aflibercept or EGFR inhibitors was permitted; treatment with other VEGF-targeting drugs (e.g., regorafenib, ramucirumab, or other tyrosine kinase inhibitors) were excluded. Patients were randomly assigned by an interactive web response system in a 2:1 ratio to receive either oral fruquintinib (5 mg/d) or matching placebo (3 weeks on/1 week off), both in combination with best supportive care. Randomization was stratified by prior use of VEGF inhibitor treatment (yes vs no) and KRAS mutational status (wild type vs mutated). Patients received treatment until disease progression, death, unacceptable toxicity, withdrawal of consent by the patient, or discontinuation by the physician. The primary endpoint was overall survival (OS). Tumor assessments were performed every 8 weeks as defined by RECIST 1.1. Key secondary endpoints were progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Duration of response (DOR) was also assessed. Assuming a median OS for placebo of 6.3 months and a mOS for fruquintinib of 9 months (HR 0.7), it was

calculated that 400 patients would be needed so that 280 overall survival events would provide 80% power to detect a difference between the 2 treatment groups, with a 2-sided p value of 0.05.

A total of 416 eligible patients were randomized in 28 sites in China to receive fruquintinib (n = 278) or placebo (n = 138) plus BSC and were included in the intention-to-treat (ITT) population. The median follow-up time was 13.3 months for the fruquintinib group and 13.2 months for the placebo group. The mean age was 54.6 years; 57% and 70% were men in the fruquintinib and placebo arms, respectively, 77% and 83% in the fruquintinib and placebo arms, respectively had primary left colorectal tumors at the time of diagnosis, 55% had wild-type KRAS tumors, 30% received prior anti-VEGF treatment, and 14% received prior anti-EGFR treatment. Median OS was 9.30 (95% CI, 8.18-10.45) months in the fruquintinib group and 6.57 (95%CI, 5.88-8.11) months in the placebo group (HR 0.65, 95% CI 0.51, 0.83; log-rank test *P* < .001). Median PFS was 3.71 (95% CI 3.65, 4.63) months vs 1.84 (95% CI 1.81, 1.84) months with placebo (HR 0.26, 95% CI 0.21, 0.34; *P* < .001). Subgroup analyses of OS were generally consistent across subgroups, except among women (HR 0.85. 95% CI, 0.57, 1.29], patients aged 65 years and older (HR 0.95, 95% CI 0.55, 1.63), or among patients with right-sided primary tumors (HR 0.96, 95% CI, 0.53, 1.75). ORR was 4.7% in the fruquintinib arm; there were no responses in the placebo arm.

Adverse events (AEs) were reported in 99% and 88% patients in the fruquintinib and placebo arms, respectively. The incidence of serious adverse events (SAEs) was 15.5% and 6% in the fruquintinib and placebo arms respectively. The most frequently reported related AEs were hypertension (55% versus 15%), palmar-plantar erythrodysesthesia syndrome (49% versus 3%), proteinuria (42% versus 25%), dysphonia (36% versus 1.5%), and thyroid stimulating hormone (TSH) increased (25% versus 2%). Grade 3-4 AEs were reported in 45% and 7% patients in the fruquintinib and placebo arms respectively. Fatal AEs were reported in 3.2% and 1.5% in the fruquintinib and placebo arms respectively.

Under IND 131038, Study 2015-013-00US1 is currently ongoing. As of the data cut-off date of September 3, 2019, 23 patients had been enrolled and received fruquintinib. Fourteen patients were enrolled in the dose escalation phase (7 patients at 3 mg once daily [QD] [cohort expanded due to a dose limiting toxicity [DLT] of Grade 4 hypertension], 7 patients at 5 mg QD, in 3 weeks on/1week off [28-day] cycles). An additional 6 patients were enrolled in a planned expansion cohort of patients with advanced, refractory solid tumors at 5 mg QD. The study was amended on December 2019 and January 2020 to add additional patients (up to 128 patients) and expansion cohorts in 40 patients with mCRC with prior treatment with regorafenib and/or TAS102 (Cohort B), 40 patients with mCRC who have progressed on all standard therapies but who have not received prior TAS-102 and/or regorafenib (Cohort C), 15 patients with advanced, refractory HR+/HER2- metastatic breast cancer (Cohort D), and 15 patients with triple-negative breast cancer (Cohort E).

The toxicity profile of patients in the 2015-013-00US1 study appeared consistent with that of other clinical studies of fruquintinib. All patients reported AEs and 83% reported Grade ≥3 AEs. The most frequently reported treatment-related AEs (per the briefing package) were hypertension (43.5%), proteinuria (35%), decreased appetite (30%), diarrhea, nausea, dysphonia, fatigue (26% each), and constipation (22%).

To support approval in the U.S. for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy, Hutchison MediPharma plans to conduct Study 2019-013-GLOB1, a multicenter, international, randomized, double-blind, placebo-controlled study of fruquintinib plus BSC versus placebo plus BSC in patients with refractory mCRC. Refractory is defined as progression on, or intolerance to, TAS-102 or regorafenib.

A total of 522 patients will be randomized (2:1) to:

- Fruquintinib 5 mg oral QD plus BSC, 3 weeks on, 1 week off
- Placebo 5 mg oral QD plus BSC, 3 weeks on, 1 week off

Randomization will be stratified by:

- Prior therapy with TAS-102 versus regorafenib versus both
- RAS status (wild type versus mutant)
- Duration of metastatic disease (≤18 months versus >18 months)

Tumor assessments will be conducted every 8 weeks until there is progression of disease (PD), death, intolerable toxicity, or withdrawal of informed consent. Safety parameters will include AEs, laboratory changes, vital signs, electrocardiogram (ECG), and echocardiogram changes.

The primary efficacy endpoint is OS in the ITT population. Secondary endpoints are PFS, ORR, DCR, DOR, duration of stable disease, assessments of safety and tolerability, characterization of PK, etc. Assuming the median OS is 6.8 months in the experimental arm and 5 months in the control arm, a total of 364 OS events are needed to detect an OS hazard ratio of 0.73 with 80% power at a 1-sided alpha level of 2.5%.

The primary analysis for OS and PFS will be a stratified log-rank test performed on the ITT population. Comparison of DCR and ORR between treatment groups will be performed using the stratified Cochran-Mantel-Haenszel test. A sequential testing procedure is proposed to adjust for multiplicity in testing OS and PFS; no adjustment is proposed for DCR and ORR.

One interim futility analysis will be conducted when 1/3 of the total number of OS events have occurred. OS will be analyzed when 364 OS events have been observed, which is expected to occur approximately 7 months after the end of enrollment. An attempt will

be made to enroll a minimum of 262 patients in a post-TAS-102 subpopulation, which must be at least 50% of the overall ITT population. The Sponsor states they have an interest in evaluating OS in the subgroup of patients who were previously treated with TAS-102 but did not receive regorafenib.

The meeting package also contains information regarding other randomized fruquintinib studies in 739 patients with advanced solid tumors, including CRC.

DISCUSSION

Clinical/Statistics

1. *Does the Agency agree that the clinical safety and efficacy data from the randomized, double-blind, placebo-controlled phase 3 study, FRESCO, which supported the approval of fruquintinib in mCRC in China, in addition to data from the ongoing phase 1/1b study 2015-013-00US1 in the US, collectively support the initiation of the proposed pivotal phase 3 study 2019-013-GLOB1?*

   FDA Response: Yes, FDA agrees.

   Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

   Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

2. *Does the Agency agree with the proposed study design of Study 2019-013-GLOB1?*

   FDA Response: Yes, FDA generally agrees. FDA recommends revising the protocol so that patients for whom molecularly targeted therapies are available (e.g., patients with MSI-H/dMMR or RAS wild-type tumors) will have received targeted therapies prior to being enrolled in Study 2019-013-GLOB1. Alternatively, ensure that the Informed Consent Document states that by enrolling into the study, patients may be foregoing treatment with proven clinical benefit.

   Additionally, given that the in vitro data show P-gp and BCRP inhibition, and pH dependent solubility, revise the protocol to address these potential drug-drug interaction (DDI) risks. This may include additional PK or other specific cohorts to assess the drug interaction potential within the proposed trial.

Provide justification for enrolling only patients with normal hepatic and renal function. Consider enrollment of patients with a wider range of renal and hepatic impairment to conduct population PK analysis and inform labeling and dosing in these patient groups.

Modify the protocol to include additional sparse PK sampling throughout the treatment period to allow for population PK analyses and exposure response analyses for safety and efficacy in the proposed patient population.

Upon submission of a complete study protocol, additional comments may be issued. Please see FDA response to Question 3 for additional comments.

Hutchison MediPharma response, received via email on February 4, 2020:

1. *Subject Inclusion Criteria*

   The inclusion criteria found in Section 5.3 of the phase 3 protocol states that subjects with RAS wild-type tumors will be enrolled only if they have been previously treated with approved anti-EGFR therapies (Inclusion criteria #4). The inclusion criteria will be revised to reflect that subjects with MSI-H/dMMR tumors must have received approved targeted therapies prior to being enrolled in Study 2019-013-GLOB1 if deemed appropriate by the treating physician.

2. *P-gp and BCRP Substrate*

   The company acknowledges that fruquintinib has the potential to inhibit P-gp and BCRP based on in vitro data. The potential DDI risk with P-gp and BCRP substrates is addressed in “Section 7.5.3 Drug-Drug Interactions” of the current phase 3 Study 2019-013-GLOB1 protocol as follows:

   “In vitro, fruquintinib is shown to have the potential to inhibit P-gp and BCRP (see Section 2.1.2.2). Avoid concomitant use with medications that are sensitive substrates of P-gp or BCRP where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the P-gp or BCRP substrate medication. Examples of the medications that are sensitive substrates of P-gp and BCRP are listed in Appendix 3.”

   The company has determined that strict prohibition of P-gp or BCRP substrates during the study is not necessary because the risk of a clinically relevant interaction with substrates of intestinal Pgp or BCRP is expected to be low based on the estimated Igut/IC50 ratio. In vitro, fruquintinib inhibited P-gp and BCRP mediated efflux with IC50 values of 4.6 μM and 1.3 μM, respectively. Using a calculated gut concentration of

50.8 µM (i.e. Igut) at a dose of 5 mg, Igut/IC50 ratio is approximately 11 for P-gp and 39 for BCRP, which is slightly above the cutoff value of 10. For P-gp, the likelihood of a clinically relevant interaction (>25% change in AUC) appears to be low when Igut /IC50 ratio is <45 according to the literature (Agarwal et al. J Clin Pharmacol 2013; 53:228 –233, Ellens et al. Drug Metab Dispos 2013; 41:1367-74). The same is expected for BCRP substrate.

Please see company's response to FDA comment for Question 7 regarding the plan to conduct a drug interaction trial to assess the effect of fruquintinib on PK of P-gp substrate and BCRP substrate.

3. *pH-Dependent Solubility*

The planned phase 3 protocol will be revised to restrict patients from using proton pump inhibitors during the study. If concomitant use of an acid-reducing agent is unavoidable, H2-antagonist may be used but should be administered 10 hours before or 2 hours after fruquintinib.

4. *Patients with Hepatic and Renal Function*

In the planned phase 3 protocol, patients with mild hepatic impairment are permitted. Per protocol, patients with total bilirubin >1.5 x upper limit of normal (ULN) and ALT or AST > 2.5 x ULN in patients without liver metastases and AST or ALT > 5 x ULN in patients with liver metastases are excluded (mild hepatic renal impairment is defined as total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST according to NCI criteria). Similarly, patients with mild renal impairment (CrCL: 60-90 mL/min) are permitted to participate in the proposed trial. This is consistent with the enrollment criteria for the FRESCO study.

The company is planning to conduct separate clinical trials to evaluate fruquintinib PK in subjects with moderate (CrCL: 30 to 59 mL/min) or severe (CrCL: 15 to 29 mL/min) renal impairment and in subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment to inform labeling and dosing in these patient groups (see Table 19 of the meeting information package). Given the 26% incidence of AST increases seen in clinical studies, the effect of severe hepatic impairment on the PK of fruquintinib will not be studied as it is unlikely to be tolerated in this patient population.

5. *Pharmacokinetic Sampling*

The company is of the opinion that the PK sampling scheme in the planned protocol has sufficient number of samples to allow for population PK and exposure-response analyses. PK samples will be collected on Days 1 and 21 of Cycles 1 through 3, which will provide 16 PK samples for each patient (n=522) (see details in Table 2: Schedule of Assessment for PK and ECG Evaluations). Based on a randomization ratio of 2:1, approximately 5568 samples will be available from 348 patients treated with fruquintinib for the analyses. The planned PK sampling scheme covers fruquintinib PK after the first dose, after multiple doses at steady-state over 3 treatment cycles, as well as trough concentrations after the 1-week off treatment period. This is consistent with sparse PK sampling scheme used for other small molecule TKIs that follow the same 3-week on/1-week off dosing schedule (e.g. regorafenib) to allow for population PK and exposure-response analyses (Solms et al. Eur J Pharm Sci 2017; 109S:S149-S153, Bekaii-Saab et al. Lancet Oncol 2019; 20:1070-1082). The company considers that the planned PK sampling scheme as proposed is sufficient and believes that additional sparse PK samples throughout the treatment period may impose unnecessary burden on both mCRC patients and study personnel.

Does the Agency agree that the company's plans outlined above adequately address the FDA comments?

Discussion during the meeting: FDA agreed that patients with mild hepatic impairment could be enrolled into the proposed randomized clinical trial.

FDA stated that Hutchison MediPharma could expand the eligibility criteria to allow for the enrollment of patients with renal impairment into the trial. Otherwise, Hutchison MediPharma may need to conduct a dedicated renal impairment study to assess for the effects of fruquintinib in patents with renal impairment.

FDA also stated that it may be acceptable for sicker patients (e.g., with respect to renal or hepatic impairment) to enroll into the proposed study; however, the primary analyses of efficacy could exclude these patients. If Hutchison MediPharma considers this approach, Hutchison MediPharma should clearly pre-specify (at enrollment) how these patients would be excluded from the primary analysis.

FDA generally agreed that Hutchison MediPharma's plans with respect to drug-drug interactions and proton pump inhibitors appeared acceptable.

Hutchison MediPharma stated that they plan to collect PK samples from all patients after the first dose of fruquintinib and at steady state during three

different cycles. FDA recommended, however, collection of sparse samples throughout treatment to allow for E-R analyses to be conducted. FDA stated that recommended approaches for sparse sampling are provided for in FDA Guidance. FDA confirmed that dense sampling would not need to be conducted in all patients.

3. *Does the Agency agree with the statistical assumptions underlying the study design and the analysis plan for the proposed phase 3 study, 2019-013-GLOB1?*

FDA Response: In general, FDA does not object to the proposed statistical analysis plan. FDA will consider the Cochran-Mantel-Haenszel tests of ORR and DCR as exploratory analyses because the tests were not planned for controlling the overall false positive rate at the two-sided alpha level of 0.05. Additionally, DCR has not been accepted by the Agency as a measure of clinical benefit for product labeling as delay in progression is better captured by PFS as a time-to-event analysis.

Specify the detailed futility criteria at the interim analysis in the protocol.

Please provide a detailed definition for the post-TAS-102 subpopulation and the detailed enrollment strategy for the minimum of 262 patients in this subpopulation in the protocol. Note that a specific claim of treatment effect in a particular subgroup requires pre-specification of the corresponding null hypothesis, control of alpha, and an appropriate confirmatory analysis strategy. Otherwise, FDA will consider the subgroup analysis exploratory.

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the Agency's comments regarding ORR and DCR to be considered exploratory analysis in the absence of multiplicity adjustment.

The phase 3 protocol will be revised to incorporate the information listed below to address the FDA comments:

- additional details regarding futility criteria at the interim analysis
- detailed definition for the post-TAS-102 subpopulation
- enrollment strategy for the minimum of 262 patients in the post-TAS-102 subpopulation

Does the Agency agree that the company's plans outlined above adequately address the FDA comments?

Discussion during the meeting: Preliminarily, FDA did not object to the proposed approach and would review the proposal when submitted to the IND.

4. *Given the strong efficacy with acceptable safety data from the China phase 2 and phase 3 FRESCO studies together with on-going US phase 1/1b study, would the Agency consider a more expedited regulatory approval pathway, with the proposed phase 3 study or an interim efficacy analysis serving as the confirmatory trial to support an NDA?*

FDA Response: Based on the information provided in the meeting package, it is unlikely that the results of Studies 2012-013-00CH1 and FRESCO would be adequate to support a marketing application for fruquintinib. For example, it appears that the results of these studies have limited applicability to the U.S. population who will have received a different spectrum of prior therapies (this was also expressed by the authors of the FRESCO study in JAMA Oncology). Furthermore, the on-going U.S. study would only provide limited safety and PK data (endpoints such as DCR or PFS would not be interpretable in a single arm trial).

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

5. *Does the Agency agree with the proposal to submit results from the 2019-013-GLOB1, the 2015-013-00US1, and the FRESCO studies to support an indication for fruquintinib for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if RAS wild-type, an anti-EGFR therapy?*

FDA Response: FDA agrees that if the results of the FRESCO study are confirmed in Study 2019-013-GLOB1, the totality of the data would support submission of an NDA for the proposed population.

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

6. *Does the Agency agree with the plan to submit an initial pediatric study plan (iPSP) requesting a full waiver for pediatric studies for fruquintinib?*

FDA Response: FDA acknowledges Hutchison MediPharma's proposal to submit an initial pediatric study plan (iPSP) with plans to request a full waiver for fruquintinib for a colorectal cancer indication. Although an iPSP must be submitted within 60 days of this meeting (see below PREA requirements), be advised that under Section 505B of the FD&C Act as amended by Title V of the FDA Reauthorization Act of 2017 (FDARA), any original marketing application for a drug or biological product with a new active ingredient that is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, if submitted on or after August 18, 2020, must contain reports of molecularly targeted pediatric cancer investigations unless a deferral or waiver of that requirement is granted. If FDA determines that the molecular target of fruquintinib meets these criteria, and Hutchison MediPharma intends to submit a marketing application on or after August 18, 2020, Hutchison MediPharma will need to submit an amended Agreed Initial Pediatric Study Plan as soon as possible and prior to the submission of an NDA for fruquintinib.

The amended iPSP would need to include molecularly targeted pediatric cancer investigation(s) that Hutchison MediPharma plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach) or any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation.

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

Clinical Pharmacology

7. *Does the Agency agree that data from the completed clinical pharmacology studies presented in this package (Table 18), along with the planned studies and additional analyses (Table 19), will be sufficient to support an NDA for fruquintinib?*

FDA Response: To assess whether the package will be acceptable, provide a plan to assess the effect of fruquintinib on the exposure of P-gp and BCRP substrates within 30 days of the current meeting. It is FDA's expectation that these effects of fruquintinib will be assessed prior to initial NDA submission. Once data are available from the planned clinical studies with strong CYP3A

inhibitors and inducers, assess the need for assessment of the effect of moderate inhibitors and inducers via clinical studies or PBPK modeling and include the analysis in the planned NDA submission. Additionally, provide the plan for assessing the QT prolongation potential of fruquintinib for FDA review and comment within 30-days of the current meeting. With the QT plan, submit the Clinical Pharmacology Table 1: *IRT's Highlights of Clinical Pharmacology and Cardiac Safety,* that is included in Additional Comment 13 below.

Hutchison MediPharma response, received via email on February 4, 2020:

1. *P-gp and BCRP Substrates*

   The company acknowledges that the potential for fruquintinib to impact the absorption of concomitant P-gp and/or BCRP substrates cannot be ruled out based on the calculated Igut/IC50 ratios although the likelihood of a clinically relevant interaction (>25% change in AUC) seems low (see company's response to FDA comment for Question 2). To evaluate the clinical relevance of in vitro findings, the company will conduct a clinical study in healthy volunteers with a substrate of P-gp (e.g. dabigatran) and BCRP (e.g. rosuvastatin) to support the NDA submission. The proposed study will be open label and consist of 2 standalone parts. In part 1, volunteers will receive single dose of a P-gp substrate drug alone in Period 1 (reference) and with single dose of fruquintinib 5 mg simultaneously in Period 2 (test). In part 2, volunteers will receive single dose of a BCRP substrate drug alone in Period 1 (reference) and with single dose of fruquintinib 5 mg simultaneously in Period 2 (test). Periods 1 and 2 will be separated by a washout period to be determined based on the half-life of the transporter substrate. Single dose administration of fruquintinib is considered sufficient to characterize its inhibitory effect on intestinal absorption of transporter substrate according to the literature [Shimizu et al. Br J Clin Pharmacol 2006; 62:372–376, NDA 022512 (Drugs@FDA)].

2. *Effect of Moderate CYP3A Inhibitors and Inducers*

   The company acknowledges the agency's feedback and will assess the need to evaluate the effect of moderate inhibitors and inducers via PBPK modeling once data are available from the planned clinical studies with strong CYP3A inhibitors and inducers.

3. *QT Prolongation Assessment Plan*

   The plan to assess the QT prolongation potential of fruquintinib is summarized below, which can be found in Section 15.4.1 of the briefing book (see page 63). Similarly, the table of highlights of clinical

pharmacology and cardiac safety can be found in Appendix 5 of the briefing book. For convenience, it is included in Table 1 of this response document. Fruquintinib has an IC50 value of 20.9 µM (8222 ng/mL) for the human ether-à-go-related gene (hERG) assay (see Section 15.5.1.4), which is 464 times the human steady-state unbound Cmax for the proposed 5 mg QD 3 weeks on/1 week off regimen (total concentration, 385 ng/mL; unbound concentration, 17.7 ng/mL). This indicates no significant inhibitory effect on the hERG potassium channel at clinically relevant exposures. Fruquintinib had no significant impact on the respiratory or cardiovascular systems in anesthetized Beagle dogs in toxicity studies at single doses up to 1000 mg/kg and in long-term studies at doses up to 0.3 mg/kg QD. Safety ECG data collected to date in studies 2009-013-00CH1, 2012-013-00CH3, and 2012-013-00CH2 did not indicate any clinically significant ECG changes.

Using a thorough QT (TQT) study to evaluate the potential of fruquintinib to prolong the corrected QT (QTc) interval poses the following challenges:

- Given the significant accumulation of fruquintinib (~2- to 4-fold) and the major metabolite M11 (~20-fold), it would be necessary to collect ECG measurements after steady state attainment or at single doses well above the 1 to 6 mg range that has been tested. However, only single doses up to 5 mg have been tested in healthy subjects, precluding the use of healthy volunteers in a TQT study.

- Toxicity precludes testing of supratherapeutic doses even in patients. The highest dose tested to date has been 6 mg QD (continuous dosing for 4 weeks or 3 weeks on/1 week off). In Study 2009-013-00CH1, 7 patients received fruquintinib at 6 mg QD 3 weeks on/1 week off, only a slightly higher dose than the 5 mg QD 3 weeks on/1 week off. Of these patients, 1 experienced a DLT. No patients experienced a DLT at the 5 mg dose level. Therefore, doses greater than 6 mg are not supported by existing safety data.

To address regulatory requirements (ICH E14, 2005; ICH E14, 2015), a concentration-QTc modeling approach based on paired concentration and QTc data collected from approximately 120 subjects (80 fruquintinib, 40 placebo) in the planned phase 3 study (2019-013-GLOB1) at 5 mg QD 3 weeks on/1 week off will be used to evaluate the QT prolongation potential of fruquintinib. Triplicate ECG data will be collected at baseline and after the first dose on Cycle 1 Day 1 and at steady-state on Cycle 1 Day 21 from standard 12-lead ECGs or Holter monitoring and will be centrally read. Time-matched PK samples for measurement of fruquintinib and M11 concentrations will also be collected. The PK-ECG sampling will include measurements at the Tmax of both fruquintinib and M11. These data will

be used to develop concentration-QTc models to evaluate the QT prolongation potential of fruquintinib and M11. A sufficient number of paired concentration-QTc measurements will be collected to permit a robust evaluation; each subject will have 10 ECG and PK timepoints in total: pre-dose, 1, 2, 3, and 4 hours post-dose on day 1 (after the first dose) and day 21 (steady-state). Supportive categorical analyses will also be performed. Safety ECGs will be collected on Day 21 of Cycles 2 and 3, then as clinically indicated thereafter.

Does the Agency agree that the company's plans as outlined above adequately address FDA's comments and that the updated package will be sufficient to support an NDA for fruquintinib?

Discussion during the meeting: FDA agreed with the proposal that Hutchison MediPharma will conduct a study to assess for the potential of DDI risk with P-gp and BCRP substrates. FDA expressed concern, however, regarding the proposal to only assess the DDI effects after one dose of fruquintinib. Hutchison MediPharma asked FDA whether PK modeling can provide additional information to support the proposal. FDA stated that the Agency would review the justification when submitted to the IND regarding a single dose approach in healthy volunteers versus a potential multiple dose approach in patients with cancer.

FDA agreed with Hutchison MediPharma's approach to assess the need for conducting a further assessment with respect to moderate CYP3A4 inhibitors or inducers after reviewing the results of the DDI study with strong CYP3A4 inhibitors or inducers.

Regarding the QT proposal, the preliminary approach appeared acceptable; however, FDA will provide a written response either as an addendum to this meeting or under separate cover.

Post-meeting addendum: The proposal to characterize the effect of fruquintinib on the QT/QTc interval in the planned study appears acceptable. FDA has the following comments to consider when preparing the QT assessment plan and report:

a. According to Hutchison MediPharma's response to FDA's preliminary meeting comments, only a subgroup of the study population will be involved in the QT assessment (n=120). Hutchison MediPharma should describe the selection criteria for enrolling this sub-population for the QT assessment.

b. For exposure-response analyses, FDA recommends that the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J

Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

c. Include a by-timepoint central tendency analysis to support the proposed concentration-QTc analysis.

d. When Hutchison MediPharma submits the QT evaluation report, indicate whether the treatments used as part of best-supportive-care could prolong the QTc interval or increase exposure to fruquintinib. FDA recommends that Hutchison MediPharma record whether these patients receive concomitant therapy that can prolong the QTc interval.

e. Provide a brief narrative for any subject who experiences QTc >500 ms or a change from baseline QTc >60 ms. The narrative should describe whether the subject was taking any concomitant medications that prolong the QTc interval or increase the exposure to fruquintinib, and whether the subject had electrolyte imbalances or cardiac risk factors for QTc prolongation.

f. When Hutchison MediPharma submits the QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).

Nonclinical

8. *Does the Agency agree that data from the completed toxicology program, in addition to the robust clinical safety data from completed and ongoing clinical trials, support initiation of the proposed phase 3 (2019-013-GLOB1) study?*

FDA Response: Yes, the completed toxicology program appears sufficient to support initiation of the proposed study.

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

9. *Does the Agency agree that the proposed bridging study to be conducted in compliance with US Good Laboratory Practice (GLP) standards, in addition to the completed toxicology program, will support an NDA submission?*

FDA Response: The proposed bridging study and completed toxicology program appear sufficient to support an NDA submission; however, the acceptability of data from these studies will be determined during review of all data included in the NDA submission. FDA recommends auditing the completed general toxicology studies conducted under China GLP regulations that will be used to support an NDA submission and to document deviations from the US GLP regulations described in 21 CFR part 58, including the impact of these deviations on each study.

Based on Hutchison MediPharma's description of positive findings in embryo-fetal toxicity studies, conducting additional embryo-fetal toxicity studies may not be warranted. A final determination on the acceptability of the completed embryo-fetal toxicity studies will be a review issue.

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA response and has no additional comments.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

ADDITIONAL COMMENTS

Patient Report Outcomes

10. Patient-Reported Outcome (PRO) and other clinical outcome assessment data will be carefully reviewed as part of the overall benefit-risk assessment of a regulatory submission and should be collected diligently with this in mind. While not regulatory requirements, the following comments are provided to maximize the quality and interpretability of PRO data. FDA recommends collecting and separately analyzing the following patient-reported core concepts: Symptomatic adverse events; Physical function; and Disease-related symptoms (where appropriate). Additional PRO or functional measures that are important to patients could be considered based on the context of a given clinical trial, although parsimony is advised to minimize patient burden and improve the quality of data collected.

11. The following should be considered for PRO Instrument:

    a. Support the PRO instrument(s) intended for use with available data and/or published peer-reviewed literature guided by the principles laid out in the

2009 FDA Guidance for Industry entitled “Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” found at www.fda.gov/downloads/Drugs/Guidances/UCM19328.

b. In some cases, subscales or subsets of items from existing instruments may be utilized if prospectively defined and psychometrically evaluated. Early consultation with FDA is strongly recommended regarding selection of appropriate measurement tool(s) for a particular clinical trial. Some suggestions for the measurement of the patient-reported core concepts are provided below:

I. Symptomatic adverse events (AEs): FDA considers the National Cancer Institute’s PRO version of the common terminology criteria for adverse events (PRO-CTCAE) found at http://healthcaredelivery.cancer.gov/pro-ctcae/ to be a promising instrument. Provide a rationale for the selection of symptomatic adverse events that will be assessed.

II. Physical function: FDA remains open to proposals for new and existing measures of physical function in cancer patients. One option that may be considered is use of the PROMIS® physical function item bank found at http://www.nihpromis.org/measures/measureshome.

III. Disease-specific symptoms: Where appropriate and feasible, items of interest may include disease-specific symptoms that patients have reported as being important across advanced cancer settings, such as pain, anorexia, and fatigue, either individually, or within a composite "symptom score" with other important disease-specific symptoms (e.g. dyspnea and cough in lung cancer). Because measurement of time to symptom deterioration is challenging, consider enriching for symptomatic patients in the current trial or in a separate trial to measure symptom improvement.

12. The following should be considered for trial design:

a. Optimize the frequency and timing of assessments. Increased assessments early in therapy can maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.

b. Prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and

included in the analysis dataset.

c. Where feasible, analyze measures of disease-related symptoms, symptomatic adverse events, and physical function as distinct concepts.

d. Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s).

e. Carefully record the use of concomitant medications that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain).

Hutchison MediPharma response, received via email on February 4, 2020: The company acknowledges the FDA comments and will incorporate appropriate PRO instruments in the phase 3 protocol, ensuring that the frequency and timing of assessments is adequate to analyze and interpret the PRO data. Analysis of PRO data will be pre-specified in the analysis plan. PRO data will supplement the Quality of Life measures planned with validated EORTC QLQ-C30 and EQ-5D-5L Questionnaires that have also been used in pivotal trials in mCRC.

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

Clinical Pharmacology

13. Complete the following table and submit it with a QT/QTc evaluation plan for FDA review and comment. See Clinical Pharmacology Comment 7 above.

Table 1. IRT's Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen	
Maximum tolerated	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra- therapeutic dose.	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

Hutchison MediPharma response, received via email on February 4, 2020: See company's response to Question 7.

Table 1 Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic Dose and Exposure	Fruquintinib 5 mg once daily (QD) 3 weeks on/1 week off (4-week cycle) is the clinical dose for the treatment of refractory metastatic colorectal cancer (mCRC) Study 2009-013-00CH1 (Patients from China with malignant solid tumors) Single dose 5 mg: Maximum plasma concentration (C_{max}) (mean [standard deviation; SD]) = 195 (34.2) ng/mL Area under the plasma concentration-time curve (AUC) from time 0 to infinity (AUC_{inf}) (mean [SD]) = 8417 (907) ng*h/mL Study 2015-013-00US1 (Patients from the United States (US) with advanced solid tumors) Steady-state 5 mg QD 3 weeks on/1 week off: C_{max} (mean [SD]) = 385 (74.1) ng/mL AUC over dosing interval (AUC_{tau}) (mean [SD]) = 7530 (1820) ng*h/mL
Maximum Tolerated Dose	Not determined in healthy subjects. The highest single dose administered to healthy subjects was 5 mg. Multiple doses have not been administered to healthy subjects. Study 2009-013-00CH1 (Patients from China with malignant solid tumors): The maximum tolerated dose (MTD) in patients was 4 mg QD continuous dosing for 4 weeks or 6 mg QD 3 weeks on/1 week off per cycle (each cycle is 28 days).
Principal Adverse Events	Pooled studies: The most common treatment-emergent adverse events (TEAEs) (reported in ≥ 10% of fruquintinib-treated Chinese patients in a pooled safety dataset from 4 completed randomized, placebo-controlled studies of fruquintinib (Studies 2012-013-00CH1, 2013-013-00CH1, 2014-013-00CH1 and 2015-013-00CH1) were palmar-plantar erythrodysesthesia (PPE) syndrome (48.7%), hypertension (44.4%), proteinuria (31.3%), dysphonia (27.1%), blood thyroid-stimulating hormone (TSH) increase (26.3%), diarrhea (20.4%), weight decreased (17.5%), decreased appetite (17.5%), aspartate aminotransferase (AST) increased (15.8%), stomatitis (15.8%), hypothyroidism (15.6%), alanine aminotransferase (ALT) increase (13.4%), cough (12.6%), blood bilirubin increased (12.2%), fatigue (11.1%) and asthenia (10.6%). Study 2009-013-00CH1 (Patients from China with malignant solid tumors); N=40: The dosing-limiting toxicities (DLTs) (grade 3 or 4 events) were as follows: 6 mg QD continuous dose: 2 adverse events (AEs) of PPE; 5 mg QD continuous dose: 1 AE of PPE and 1 AE of thrombocytopenia with increased bleeding; 4 mg QD continuous dose: 1 AE of increased transaminase with bilirubin; 6 mg QD 3 weeks on/1 week off: 1 AE of fatigue. Study 2015-013-00US1 (Patients from the US with advanced solid tumors); N=23:

Table 1 Highlights of Clinical Pharmacology and Cardiac Safety

	TEAEs with grade ≥ 3 in ≥ 10% of fruquintinib-treated patients were the following: 3 mg QD 3 weeks on/1 week off: 2 AEs of hypertension and 1 AE of dyspnea 5 mg QD 3 weeks on/1 week off: 5 AEs of hypertension, 4 AEs of fatigue, 1 AE of vomiting, 1 AE of dyspnea, and 1 AE of uncoded.	
Maximum Dose Tested	Single Dose	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): 6 mg
	Multiple Dose	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): 6 mg QD continuous dosing
Exposures Achieved at Maximum Tested Dose	Single Dose (Mean [SD])	C_{max} = 182 (22.6) ng/mL AUC_{inf} = 8885 (966) ng*h/mL
	Multiple Dose (Mean [SD])	C_{max} = 424 (14.1) ng/mL AUC_{tau} = 8109 (563) ng*h/mL
Range of Linear PK	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): 1 to 6 mg	
Accumulation at Steady State	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): Approximately 3-fold (QD dosing)	
Metabolites	Study 2015-013-00CH2 (Healthy subjects from China): M11, which possesses inhibitory activity against vascular endothelial growth factor receptor (VEGFR) but is less potent compared to fruquintinib, is the major metabolite. Mean M11-to-^{14}C-radioactivity AUC ratio is 17% after single dose. Study 2015-013-00US1 (Patients from the US with advanced solid tumors): Mean M11-to-fruquintinib AUC ratio is about 41% at steady state.	
Absorption	Absolute/Relative Bioavailability	Not available
	Time to Reach Maximum Plasma Concentration (T_{max}) (Median [Range])	Study 2015-013-00US1 (Patients from the US with advanced solid tumors): Fruquintinib: 1.95 (0.917 - 25.0) hours Metabolite M11: 24.8 (20.2 - 25.4) hours
Distribution	Apparent Volume of Distribution (V_d/F) (Mean [SD])	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): Fruquintinib: 42.2 (9.50) L
	% Bound	95.4% protein bound
Elimination	Route	Study 2015-013-00CH2 (Healthy subjects from China): Mass balance: 60.3% in urine, 29.8% in feces; 0.5% and 5.34% of fruquintinib excreted unchanged in urine and feces, respectively
	Enzymatic Pathway	Predominantly cytochrome P450 (CYP)3A, with minor contribution of CYP2C8, CYP2C9, and CYP2C19

Table 1 Highlights of Clinical Pharmacology and Cardiac Safety

	Terminal Half-life ($t_{1/2}$) (Mean [SD])	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): Fruquintinib: 48.5 (7.3) hours Study 2014-013-00CH5 (Healthy subjects from China): Fruquintinib: 25.5 (5.3) hours Metabolite M11: 57.9 (22.8) hours
	Apparent Clearance (CL/F) (Mean [SD])	Study 2009-013-00CH1 (Patients from China with malignant solid tumors): Fruquintinib: 10.0 (1.10) mL/min Study 2014-013-00CH5 (Healthy subjects from China): Fruquintinib: 14.5 (2.02) mL/min Metabolite M11: 47.5 (20.5) mL/min
Intrinsic Factors	Age	Not available (to be evaluated using population pharmacokinetic [PK] approach)
	Sex	Not available (to be evaluated using population PK)
	Race	Not available (to be evaluated using population PK)
	Hepatic and Renal Impairment	Not available (to be evaluated with dedicated studies and population PK)
Extrinsic Factors	Drug Interactions	Not available; studies with a strong CYP3A inhibitor (itraconazole), strong CYP3A inducer (rifampin); and an acid-reducing agent (pantoprazole) are planned.
	Food Effects	Study 2012-013-00CH2 (Healthy subjects from China): Co-administration of a high-fat meal with 4 mg fruquintinib delayed fruquintinib T_{max} by 2.6 hours, decreased fruquintinib C_{max} by 17%, but had no effect on AUC. A food effect study with 5 mg fruquintinib is planned.
Expected High Clinical Exposure Scenario	Not available; studies on hepatic impairment and drug-drug interaction with CYP3A4 inhibitors are planned.	
Preclinical Cardiac Safety	The half maximal inhibitory concentration (IC_{50}) of fruquintinib on the human ether-related a-go-go gene (hERG) potassium channel was 20.9 µM (8222 ng/mL), which is about 464× the unbound human steady-state C_{max} for 5 mg QD 3 weeks on/1 week off (17.7 ng/mL), indicating no significant inhibitory effect on the hERG potassium channel. Fruquintinib had no significant impact on the respiratory or cardiovascular systems in anesthetized Beagle dogs following single doses over the dose range 0.085 to 0.34 mg/kg or at a single dose of 1000 mg/kg (using the maximum dose method). No drug-related abnormal changes were found in	

Discussion during the meeting: FDA acknowledged Hutchison MediPharma's response; there was no further discussion of this item during the meeting.

PREA REQUIREMENTS

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

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

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

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

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

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] to ensure open lines of dialogue before and during their drug development process.

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

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.[5]

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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[6] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data 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 page[7] 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 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.[8] 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

[6] https://www.fda.gov/media/88173/download
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[9] (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.[10] 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.[11]

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 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

[9] https://www.fda.gov/media/88173/download
[10] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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 Resources[12] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[13]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[14]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[15]

[12] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[13] https://www.fda.gov/media/109533/download
[14] http://www.fda.gov/ectd
[15] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

SECURE EMAIL COMMUNICATIONS

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[16]

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

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

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.

ONCOLOGY PILOT PROJECTS

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

- RTOR[17]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[18]

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

Hutchison MediPharma Ltd. provided a meeting agenda, entitled "IND131038 12Feb20 Revised Agenda.pdf," and a document, entitled "IND131038_Response to FDA Prelim commentsEOP2.pdf." These documents were received via email on February 4, 2020, and formally received on February 6, 2020.

[17] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[18] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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

/s/

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