CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212327Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078286

MEETING MINUTES

Impact Biomedicines, Inc., a Subsidiary of Celgene Corporation
Attention: Kimberly Burns, MS
Senior Manager, Global Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Ms. Burns:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fedratinib (SAR302503).

We also refer to the meeting between representatives of your firm and the FDA on May 10, 2018. The purpose of the meeting was to discuss the fedratinib drug development program to support an initial New Drug Application submission.

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

If you have any questions, call Jennifer Lee, Regulatory Project Manager at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Meeting Minutes
Sponsor Response Documents

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, May 10, 2018, 3:30 PM – 4:30 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 078286
Product Name: fedratinib (SAR302503)
Indication: Treatment of (b) (4) intermediate or high-risk, primary or secondary (post-polycythemia vera and post-essential thrombocythemia) myelofibrosis (b) (4)

Sponsor/Applicant Name: (b) (4)

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Jennifer Lee, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Ann Farrell, MD – Director
Albert Deisseroth, MD, PhD – Supervisory Associate Division Director
Barry Miller, MS, CRNP - Deputy Director for Safety (Acting)
Kathy Robie Suh, MD, PhD – Clinical Team Leader
Saleh Ayache, MD – Clinical Reviewer
Laurel Menapace, MD – Clinical Reviewer
Theresa Carioti, MPH – Chief Project Management Staff
Jennifer Lee, PharmD – Regulatory Project Manager

Office of Hematology and Oncology Products/Division of Hematology Oncology Toxicology
Chris Sheth, PhD – Supervisory Pharmacologist
Pedro Del Valle, PhD – Pharmacologist

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD – Biometrics Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Stacy Shord, PharmD, BCOP, FCCP – Clinical Pharmacology Team Leader
Sriram Subramaniam, PhD – Clinical Pharmacology Reviewer

Office of Product Quality/Office of New Drug Products/Division of New Drug Products I
Sherita Mclamore-Hines, PhD – Regulatory Review Chemist
Xing Wang, PhD – Regulatory Review Chemist

Office of Medication Error Prevention and Risk Mangement/Division of Risk Management
Joyce Weaver, PharmD – Senior Drug Risk Management Analyst

SPONSOR ATTENDEES

Jay Backstrom – Chief Medical Officer
Anne Frederick – Executive Director, Regulatory Affairs
Kimberly Burns – Senior Manager, Regulatory Affairs
Paul McInulty – Vice President, Regulatory Affairs
Torsten Gerike – Senior Director, Clinical R&D
Aleksandra Rizo – Executive Director, Clinical R&D
Tymara Berry – Director, Drug Safety
Xiaolong Luo – Senior Director, Biostatistics
Gopal Krishna – Senior Director, Clinical Pharmacology
Ying Hong – Director, Pharmacokinetics
Shiva Sekhar – Senior Director, Global Project Leadership
Sekhar Surapaneni – Executive Director, DMPK
(b) (4)

1.0 BACKGROUND

Fedratinib is a Janus kinase 2 (JAK2) inhibitor that was previously placed on full clinical hold on November 13, 2013, after possible safety signals for Wernicke's encephalopathy and congestive heart failure were reported in patients enrolled in fedratinib trials. The full clinical hold was lifted on August 18, 2017, and a meeting was held on November 1, 2017, with the previous Sponsor of this IND file, Impact Biomedicines, Inc., to discuss risk mitigation strategies with respect to the clinical adverse event findings documented in the trials.

Effective February 13, 2018, Impact Biomedicines, Inc. became a wholly owned subsidiary of Celgene Corporation. The current Sponsor, Impact Biomedicines, Inc., a Subsidiary of Celgene Corporation, submitted a Pre-NDA meeting request on March 7, 2018, to discuss the fedratinib drug development program to support the initial New Drug Application (NDA) submission of fedratinib for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential

thrombocythemia myelofibrosis, (b) (4) .

FDA sent Preliminary Comments to Impact Biomedicines, Inc., a Subsidiary of Celgene Corporation on May 7, 2018.

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls

Question 1: *If the stability data from the primary stability site and the proposed commercial site are determined to be comparable, does the Agency agree with the assignment of a* (b) (4) *month period retest for drug substance commercial production?*

FDA Response to Question 1: The retest period of drug substance will be determined during the NDA review based on the totality of data submitted in the NDA application. In addition to stability data, we recommend that you provide the comparison of drug substance manufacturing process, starting materials, reagents and solvents, batch release data, container closure system, etc. The proposed commercial site should have a satisfactory current Good Manufacturing Practice (CGMP) inspection record.

Meeting Discussion: No discussion occurred.

Question 2: *If the stability data from the primary stability site and the proposed commercial site are determined to be comparable, does the Agency agree with the assignment of a 48-month shelf life for drug product commercial production?*

FDA Response to Question 2: The shelf life of the drug product will be determined during the NDA review based on the totality of data submitted in the NDA application. In addition to stability data, we recommend that you provide the comparison of drug product formulation, manufacturing process, equipment, batch size, container closure system, etc. The proposed commercial site should have a satisfactory current Good Manufacturing Practice (CGMP) inspection record.

Meeting Discussion: No discussion occurred.

2.2 Nonclinical

Question 3: *Does the Agency agree that the nonclinical safety pharmacology and toxicology program as described below and in Table 3 is acceptable for the filing of the NDA?*

FDA Response to Question 3: The nonclinical safety pharmacology and toxicology program described in the meeting package appears acceptable for filing of the NDA for fedratinib. Any final decisions on the sufficiency of the nonclinical information to support the NDA will be a review issue.

Meeting Discussion: **No discussion occurred.**

2.3 Clinical Pharmacology

Question 4: *Is the biopharmaceutical and clinical pharmacology program as described below and in Table 4 adequate to support the NDA?*

FDA Response to Question 4: No, we recommend the following additional studies or analyses be completed in support of the original NDA:

1. Conduct a clinical drug-drug interaction (DDI) study with strong CYP3A inducers.

Meeting Discussion: **The Agency encouraged the Sponsor to conduct a clinical DDI study with strong CYP3A inducers before submitting the original NDA and stated that**

(b) (4)

2. Conduct physiologically based PK (PBPK) modeling and simulation to investigate the effect of moderate CYP3A inhibitors and moderate CYP3A inducers and provide dose adjustments for fedratinib with concomitant use drugs that are moderate CYP3A or moderate to strong CYP3A inducers.

Meeting Discussion: **Celgene agreed with the Agency's proposal to develop a PBPK model to investigate the effects of moderate and weak CYP3A4 inhibitors.**

3. Conduct a clinical study to determine the effect of hepatic impairment. Refer to Question 6 for details.

4. Since fedratinib is a substrate of P-gp and inhibitor of other transporters in vitro, determine the need for in vivo drug-drug interaction (DDI) studies based on In Vitro Metabolism- and Transporter and Clinical Drug Interaction Studies FDA Guidances, and provide a study plan if the criteria for conduct of DDI studies are met.

Meeting Discussion: **The Agency agreed with the proposal to conduct DDI studies post-approval to assess the effects of fedratinib on the transport of other drugs. The Agency recommended that the Sponsor submit the protocols for review.**

The Agency recommended that the Sponsor summarize their justification for (b) (4) [redacted]. The acceptability of the absence of a clinical trial will be a review issue.

5. Identify the formulations used in each clinical study. The briefing package indicates that a relative bioavailability study was conducted between a tablet and capsule fomulation. If a different formulation(s) was used in clinical program, bridging data should be provided to support registration of fedratinib for the proposed indications.

Meeting Discussion: The Agency stated that it is important to demonstrate that the three different capsule formulations will provide similar pharmacokinetics to allow the pharmacokinetic data from all the formulations to support the original NDA submission. The Agency encouraged the Sponsor to discuss the information needed to support the comparability of the three capsule formulations during the planned pre-NDA meeting with CMC.

In addition, include the full reports and associated data sets for Studies ARD12042 and ARD12888, population PK analysis, and exposure-response analyses for efficacy and safety. Also, refer to the responses to Questions 5a, 5b, and 6, and Additional Comments 5 and 6.

Question 5a: *Does the Agency agree with Celgene's proposal that results from the dedicated QT study, TES13519, and a QTc assessment of electrocardiogram (ECG) data from a Phase 1 study, TED12037, and a Phase 3 study, EFC12153, are sufficient to support the NDA regarding a lack of risk of fedratinib's QT prolongation potential?*

FDA Response to Question 5a: We are unable to provide a response to this question at this time based on the information in the meeting background package. We refer you to previous advice we provided to you on November 7, 2017, as follows:

Submit the following data:

1. When you submit your 'thorough QT study' (TES13519) report, please include the following items:

    a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

    b. Electronic copy of the study report

    c. Electronic or hard copy of the clinical protocol

    d. Electronic or hard copy of the Investigator's Brochure

    e. Annotated CRF

f. A data definition file which describes the contents of the electronic data sets

g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses

h. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g, QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI) Lead, and ECG ID (link to waveform files, if applicable),

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

j. Narrative summaries and case report forms for any:

   i. Deaths

   ii. Serious adverse events

   iii. Episodes of ventricular tachycardia or fibrillation

   iv. Episodes of syncope

   v. Episodes of seizure

   vi. Adverse events resulting in the subject discontinuing from the study

k. A completed Highlights of Clinical Pharmacology Table

2. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).

3. Advancing in this field – and possibly reducing the burden of conducting QT studies depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://www.cardiac-safety.org/ecg-database/.

Meeting Discussion: Celgene acknowledged the Agency's response. There was no further discussion.

Question 5b: *The report for Study TES13519 is an abbreviated Clinical Study Report (CSR); however, all necessary data are available in the CSR appendices (i.e., pharmacodynamic*

response data and all safety data). Does the Agency agree that an abbreviated CSR rather than a full CSR for Study TES13519 is acceptable as part of the NDA for fedratinib?

FDA Response to Question 5b: See response to Question 5a.

Meeting Discussion: Celgene acknowledged the Agency's response. There was no further discussion.

Question 6: *Sanofi conducted a study in subjects with mild hepatic impairment (POP13450); however, fedratinib exposure has not yet been evaluated in subjects with moderate or severe hepatic impairment. Does the Agency agree that Celgene may conduct this study post-approval?*

FDA Response to Question 6: No. As stated above, conduct a clinical study to determine the effect of hepatic impairment. Alternatively, if patients with moderate and severe hepatic impairment were enrolled in the clinical trials, conduct population PK analysis using data from these patients to determine the effect of hepatic impairment. The adequacy of the popPK will be a review issue.

In addition, you should propose dosing recommendations for fedratinib for patients with severe renal impairment, and for concomitant use of moderate and strong CYP3A inhibitors and inducers in your NDA submission. Also, propose the strategy for the concomitant use of medications that are substrates of CYP3A, 2C19, or 2D6, as fedratinib increased exposure of CYP3A, 2C19, and 2D6 substrates by ≥2-fold.

Meeting Discussion: The Sponsor proposes to conduct a population PK analysis to evaluate the effect of mild and moderate hepatic impairment on the clearance of fedratinib. Based on the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, the patient population will include 251 (67%) patients with normal hepatic function, 103 (28%) patients with mild hepatic impairment, and 19 (5%) patients with moderate hepatic impairment. The Agency stated that the acceptability of the Sponsor's proposed analysis will be a review issue. The Sponsor also proposes to conduct a study in patients with severe hepatic impairment post-approval. The Agency stated that the Sponsor should include justification for conducting this study post-approval and provide a summary of the proposed clinical study, including a study synopsis and major milestones (e.g., study completion date, submission of final study report), for FDA review at the time of NDA submission.

2.4 Clinical

Question 7: *Does the Agency agree that the efficacy and safety data from the key Phase 3 study EFC12153 (JAKARTA) and the key Phase 2 study ARD12181 (JAKARTA 2) are clinically meaningful and provide an adequate basis for the filing and review of an NDA for fedratinib as a treatment for intermediate or high-risk, primary or secondary (post-polycythemia vera and post-essential thrombocythemia) myelofibrosis,* (b) (4)

(b) (4)

FDA Response to Question 7: Your proposal of Study JAKARTA-1 and Study JAKARTA-2 to support an NDA submission for the proposed indication of treatment of intermediate or high-risk, primary or secondary myelofibrosis may be acceptable. Decision on filing will be made after the application is reviewed. The adequacy of phase 3 pivotal study (JAKARTA1) and the supportive Phase 2 (JAKARTA 2) study in support of the proposed indication will be determined at the time of the review.

(b) (4)

We still have concerns regarding the development of encephalopathy associated with fedratinib treatment. Additional information regarding risk mitigation for Wernicke's Encephalopathy should be included in your NDA submission.

Meeting Discussion: The Sponsor discussed their investigative study results related to thiamine levels in rats exposed to fedratinib. The study appears to address some of the deficiencies raised at the November 1, 2017 meeting with the earlier study. The Agency agreed further non-clinical studies would not be necessary at this time.

The Agency reiterated concern for WE and emphasized that the Sponsor will need to address this in the NDA. (b) (4) **. The Sponsor described a** (b) (4) (b) (4) (b) (4) **The Agency recommended that a medication guide be included as part of the labeling.**

Regarding the (b) (4) **indication: Generally, two adequate and well-controlled trials are required for an indication. JARKARTA1 appears to be one such study for the indication. A single study may suffice provided the study is well-designed and conducted, with robust, persuasive, internally consistent results across multiple subsets.**

Adequacy of the study to support the indication will be a review issue. For the (b) (4) indication we anticipate that JAKARTA2 may provide some relevant supportive data.

(b) (4)

The Agency agreed to further discussion surrounding the JAKARTA 2 study.

Question 8: (b) (4)

(b) (4)

2.5 Biostatistics

Question 9: *The Statistical Analysis Plan (SAP) provides a detailed description of the strategy and statistical techniques to be used to perform the safety and efficacy analyses of data to be presented in the Summary of Clinical Safety (SCS)/ Integrated Summary of Safety (ISS) and Summary of Clinical Efficacy (SCE). Does the Agency have any recommendations for additional analyses or data presentations in the NDA to facilitate the assessment of efficacy and safety of fedratinib?*

FDA Response to Question 9: We do not have additional recommendations now regarding additional analyses or data presentations.

Meeting Discussion: No discussion occurred.

Question 10: *Celgene plans to submit a Summary of Clinical Efficacy (SCE) in Module 2 as part of the NDA but does not plan to prepare an Integrated Summary of Efficacy (ISE). Does the Agency agree with this proposal?*

FDA Response to Question 10: Your proposal appears to be acceptable.

Meeting Discussion: No discussion occurred.

Question 11: *Celgene plans to submit a full Integrated Summary of Safety (ISS) in Module 5 as part of the NDA (i.e., the text portion of an integrated analysis of safety plus the supporting tables and figures). A Summary of Clinical Safety (SCS) will be located in Module 2. Does the Agency agree with this proposal?*

FDA Response to Question 11: Your proposal appears to be acceptable.

Meeting Discussion: No discussion occurred.

Question 12: *All sections of the dossier will follow the electronic common technical document (eCTD) format. The legacy nonclinical and clinical electronic submission datasets (Study Data Tabulation Models [SDTMs] and the analysis data sets [ADSs]) supporting the initial NDA were initiated prior to 17 Dec 2016. Celgene intends to submit datasets based on the Study Data Specifications version published at the time of study completion to be used for the analysis of each individual study (FDA correspondence, 24 Apr 2013; eData plan, [30 May 2013, SN 0204]). Does the Agency agree with this approach?*

FDA Response to Question 12: Based on the statement this approach looks acceptable if all studies were initiated prior to 17 Dec 2016 for the NDA. Please provide more details, listing all study names, study start date, and study data that will be submitted (i.e., legacy tabulations, legacy analysis, SDTM or ADaM).

Meeting Discussion: No discussion occurred.

2.6 Safety

Question 13: *Does the Agency agree with the list of adverse events for which Celgene plans to write narratives for inclusion in the NDA?*

FDA Response to Question 13: Your proposal of the list of adverse events and narratives appear to be acceptable. CRFs for these patients should be submitted as well.

Meeting Discussion: No discussion occurred.

Question 14: *In light of the Type A Meeting Impact Biomedicines had with the FDA on 01 Nov 2017, Celgene intends to incorporate the Agency's guidance for the management of gastrointestinal adverse events and Wernicke encephalopathy in the Phase 3b study (Draft*

Protocol Synopsis) and in the proposed USPI for fedratinib. Does the Agency agree with this approach?

FDA Response to Question 14: We cannot provide definitive statements regarding the labeling, as we have not reviewed all the data.

We do not have evidence to support whether the incidence of WE related to thiamine deficiency or ineffective thiamine (inability to transport thiamine to the brain) or the risk of WE associated with fedratinib is reversible by thiamine replacement (IV vs oral).

Meeting Discussion: No discussion occurred.

2.7 Regulatory

Question 15: *Celgene plans to submit a* (b) (4) *for fedratinib for myelofibrosis patients who have failed, are intolerant to, or are ineligible for treatment with ruxolitinib, based on Study ARD12181 and the results presented in the Context/Rationale of Question 7. Does the Agency agree with this approach?*

FDA Response to Question 15: The unresolved issues regarding WE make it difficult to envision (b) (4).

Meeting Discussion: No discussion occurred.

Question 16: *Does the Agency agree with Celgene's proposal regarding the 4-Month Safety Update?*

FDA Response to Question 16: Your proposal appears to be acceptable.

Meeting Discussion: No discussion occurred.

Additional Comments

With respect to proposed Phase 3 study, the full protocol should:

1. Include patients with moderate (creatinine clearance 30 to 59 mL/min/1,73m^2) and severe renal impairment (creatinine clearance <30 mL/min/1,73m^2) with appropriate dose adjustments.

2. Include patients taking moderate and strong CYP3A inhibitors with appropriate dose adjustments. Provide PBPK modeling and simulations results to support dosing strategy with moderate CYP3A inhibitors.

3. Avoid strong CYP3A inducers in the absence of clinical data.

4. Provide risk mitigation strategy for the concomitant use of medications that are substrates of CYP3A, 2C19, or 2D6.

5. Specify that fedratinib may be taken without regard to food.

6. Include sparse PK sampling.

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

7. In the Summary of Clinical Pharmacology in your proposed NDA, address the following:

    a. Basis for selecting the dosage used in the registration trial.

    b. Exposure-safety and exposure-efficacy relationships.

    c. Assessment of the potential for fedratinib to prolong the QT/QTc interval, and the conclusion and proposed labeling description.

    d. Characteristics of absorption, distribution, and elimination.

    e. Influence of intrinsic factors (such as sex, race, weight, disease, organ impairment) and extrinsic factors (such as drug interactions, diet) on fedratinib exposure, efficacy and safety, and the recommended dose.

8. In addition, apply the following advice in preparing the clinical pharmacology sections of the original NDA submission:

    a. Submit bioanalytical methods and validation reports for all clinical pharmacology studies. Submit cross validation reports if different methods or different bioanalytical sites were used.

    b. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

    c. The patients' unique ID in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

        i. 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.

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

iii. Identify patients who were on medications that are substrates, inhibitors, or inducers of cytochrome P450 enzymes for which drug-drug interactions have been demonstrated.

d. Submit information and data to support the population pharmacokinetic analysis. Refer to the pharmacometric data and models submission guidelines found at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm and the Guidance for Industry found at. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for more information.

e. Submit the results of exposure-response (measures of effectiveness, biomarkers and toxicity) analyses for fedratinib in the to-be-indicated patient population in the NDA submission. Include an assessment of the effect of covariates on the exposure-response relationships. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that the Sponsor would provide a REMS proposal as part of their NDA submission. Please also refer to the meeting discussion for Question 7 above.

- 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.

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were identified.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's response document, a preliminary summary of the nonclinical rat study and a table containing the size of the fedratinib safety database are appended to these minutes.

APPEARS THIS WAY ON ORIGINAL

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

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

/s/

KATHY M ROBIE SUH
05/15/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78286

MEETING MINUTES

Sanofi US Services Inc.
Attention: Franklin Vairinhos, PhD
Senior Director, Global Regulatory Affairs
500 Kendall Square, 5169
Cambridge, MA 02142

Dear Dr. Vairinhos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAR302503 capsules, 100 mg.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2013. The purpose of the meeting was to discuss and obtain FDA agreement on the content of the New Drug Application (NDA) for SAR302503 to support registration for the treatment of patients with intermediate or high-risk myelofibrosis (b) (4) .

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

If you have any questions, call Theresa Carioti, Regulatory Project Manager at (301) 796-2848.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 27, 2013 1:00 – 2:00 PM ET
Meeting Location: White Oak Bldg 22, Room 1311

Application Number: IND 78286
Product Name: SAR302503
Indication: for the treatment of patients with intermediate or high-risk myelofibrosis (b) (4)

Sponsor/Applicant Name: Sanofi
Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Theresa Carioti, MPH

FDA ATTENDEES

Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Saleh Ayache, MD, Clinical Reviewer
Qin Ryan, MD, PhD, Safety Medical Officer
Diane Leaman, BS, MT (ASCP), Safety Project Manager
Theresa Carioti, MPH, Regulatory Project Manager

Office of Hematology and Oncology Products (OHOP)
Tamy Kim, PharmD, Associate Director for Regulatory Affairs
Michael Wissing, ORISE fellow

Division of Hematology Oncology Toxicology (DHOT)
Haleh Saber, PhD, Supervisory Pharmacologist
Pedro Del Valle, PhD, Pharmacology/Toxicology Reviewer

Office of Business Informatics (OBI), eData Management Solutions
Douglas Warfield, PhD, Interdisciplinary Scientist

Office of Biostatistics (OB), Division of Biometrics (DB)
Mark D. Rothmann, PhD, Statistical Team Leader
Chia-Wen Ko, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Julie Bullock, PharmD, Clinical Pharmacology Team Leader
Young-Jin Moon, PharmD, Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, MS, CMC Team Lead
Josephine Jee, PhD, CMC Reviewer

Division of Risk Management
Joyce Weaver, PharmD, BCPS, Senior Drug Risk Management Analyst

Office of Pharmacovigilance and Epidemiology, Division of Pharmacovigilance
Peter Waldron, MD, Medical Officer
Kate Coyle, PharmD, Safety Evaluator

Office of Strategic Programs
Kim Taylor, Operations Research Analyst

EASTERN RESEARCH GROUP ATTENDEES
Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES
Sanofi:
Tal Zaks, MD, PhD, Vice President, Head of Development, Oncology Division
Pamela S. Cohen, MD, Associate Vice President, Oncology Clinical Development
Claudia Lebedinsky, MD, PhD, Senior Medical Director, Oncology Clinical Development
Frank Neumann, MD, PhD, Medical Director, Oncology Clinical Development
Remi Castan, MD, Senior Director, Oncology Clinical Development
Zhenming Shun, PhD, Associate Vice President, Biostatistics Oncology
Guozhi Gao, PhD, Senior Manager, Biostatistics Oncology
Anjali Vaze, MD, Director, Global Safety Officer, Global Epidemiology and Pharmacovigilance
Jian Yin, MD, Director, Clinical and Exploratory Pharmacology
Sunil Gupta, MD, Associate Vice President, Regulatory Affairs Oncology

1.0 BACKGROUND

Sanofi submitted a request for a pre NDA meeting on April 15, 2013. The meeting request was granted on April 25, 2013 and a face-to-face pre NDA meeting was scheduled for June 27, 2013. The purpose of this meeting is to discuss and obtain FDA agreement on the content of the NDA for SAR302503 to support registration for the treatment of patients with intermediate or high-risk myelofibrosis (b) (4). The proposed indication will be supported primarily by the Phase 3 clinical trial EFC12153 (JAKARTA trial). EFC12153 is multinational, double-blind, placebo-controlled, randomized clinical trial of 2 doses of SAR302503 (400 and 500 mg daily) in myelofibrosis patients not previously exposed to a JAK2 inhibitor.

The Phase 3 registration trial, EFC12153, was reviewed under a Special Protocol Assessment (SPA) agreement (SPA granted letter issued on September 9, 2011). In addition, SPA agreement was reached on the carcinogenicity studies for the 6 month mouse study and 2 year rat study.

The Agency has also been in communication with Sanofi regarding their plans for QTc evaluation. In addition, guidance on eData Plan and Statistical Analysis Plan have been provided to Sanofi in Type C Written Response Only communication on April 24, 2013.

SAR302503 was granted orphan designation on May 18, 2009 for the treatment of secondary and primary myelofibrosis.

2. DISCUSSION

2.1 Quality

Question 1:
It is Sanofi's intention to have a complete CMC Module at the time of submission, including 12-month primary stability data on both drug substance and drug product batches.

Does the Agency agree that the attached table of contents for the CMC information (module 2.3 and module 3) together with the proposed CMC content, summarized in this briefing document, constitute a complete reviewable CMC module?

FDA Response to Question 1: Your approach is reasonable. A final determination of acceptability will be made at the time of NDA review.

Sanofi Response June 25, 2013: No further comments.

Meeting Discussion June 27, 2013: No discussion occurred.

2.2 Nonclinical

Question 2:

The non-clinical toxicity profile of SAR302503 was evaluated in a battery of general toxicology studies (single-dose and repeat-dose studies up to 6 months in rats and 9 months in dogs), in in vitro and in vivo genetic toxicity studies and in embryofetal toxicity studies in rats and rabbits. Fertility and pre- and post-natal studies in rats are on-going and will be included in the CTD.

A 6-month carcinogenicity study in transgenic (TG) mice is on-going. Sanofi plans to include the 6-month TG mouse carcinogenicity study in the NDA as a report that comprises: a QA-audited toxicology report with a signed-final histopathology report (with electronic data). The signed-final version of the full report will be provided within one-month of submission. [redacted] (b) (4)

Safety pharmacology studies included: a study of neurofunctional assessment in Sprague-Dawley rats; a study of effects on the hERG channel current expressed in mammalian cells; and a cardiovascular and respiratory study in conscious telemetered beagle dogs.

Does the Agency agree with Sanofi's proposal for submitting the report for the 6-month TG mouse study?

FDA Response to Question 2: The results of [redacted] (b) (4) **the 6-month** [redacted] (b) (4) **carcinogenicity studies may be submitted post-approval. However, if you choose to submit the 6-month mouse study with the NDA, you should submit the final study report, not a draft report.**

Sanofi Response June 25, 2013: The PDUFA V Performance Goals for 2013 provides examples of submission components that may be appropriate for delayed submission, i.e. within 30 days of submitting the NDA. This includes a final audited report of a preclinical study (e.g., carcinogenicity) provided the final draft report is submitted with the original application. This is consistent with the approach proposed above by Sanofi for the 6-month mouse study. Please confirm, therefore, that the signed-final version of the full report can be submitted within 30 days of submitting the NDA, if the QA-audited toxicology report with a signed-final histopathology report (with electronic data) is submitted with the original application.

Meeting Discussion June 27, 2013: The sponsor's proposal is acceptable.

Question 3:

Does the Agency agree that [redacted] (b) (4)

FDA Response to Question 3: Your proposal is acceptable.

Sanofi Response June 25, 2013: No further comments.

Meeting Discussion June 27, 2013: No discussion occurred.

Question 4:
Does the Agency agree that the nonclinical safety pharmacology and toxicology program (which includes the 6-month TG mouse carcinogenicity study) is acceptable for the filing of the NDA?

FDA Response to Question 4: Your proposal is acceptable; however, a decision on the adequacy of the studies will be made after review of the data submitted with the NDA.

Sanofi Response June 25, 2013: No further comments.

Meeting Discussion June 27, 2013: No discussion occurred.

2.3 Clinical

Question 5:
The emerging safety profile of JAK2, based on available Phase 1, 2 and 3 data suggests that the safety profile can be suitably managed with sufficient guidance through product labeling and pharmacovigilance surveillance, without additional risk minimization activities. It is our understanding that no other risk management documents would be required in the initial submission of the supplemental BLA application.

Therefore, the Sponsor proposes the following:

- The proposed draft label to be submitted in the NDA for JAK2 would provide an adequate representation of the overall safety profile for the drug including any identified risk mitigation/minimization steps for the key toxicities associated with the drug.
- (b) (4)

Question 5a: Does the Agency agree that a REMS proposal does not need to be included in the application?

FDA Response to Question 5a: Yes, we agree. A REMS proposal does not need to be included with the application.

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for REMS during the review of your application.

Sanofi Response June 25, 2013: No further comment.

Meeting Discussion June 27, 2013: Refer to discussion in Section 3.0 Discussion of the Content of a Complete Application.

Question 5b: Will the Agency confirm that no other risk management/ pharmacovigilance documents are expected for the submission?

FDA Response to Question 5b: The Division of Pharmacovigilance (DPV) requests inclusion in the application of any PV plans that were developed for applications to other countries. If the Sponsor has not developed such a plan, then please state that. The Agency may require additional documents if safety concerns arise during the review of the NDA application.

Sanofi Response June 25, 2013: Sanofi is preparing a Risk Management Plan (RMP) to meet EU requirements for the Marketing Authorization Application (MAA). Please confirm if the Agency is requesting inclusion of this document in the NDA, and if so, please clarify whether the complete RMP or only the Pharmacovigilance Plan module should be included.

Meeting Discussion June 27, 2013: The sponsor agrees to provide the complete RMP.

2.4 Clinical Pharmacology

Question 6:
The biopharmaceutical section of the NDA will include food effect studies with high fat and low fat meals (FED12258 and ALI13451).
The clinical pharmacology section of the NDA will include final reports for all studies listed in Table 38, except for the ongoing thorough QT (TES13519), renal impairment (POP13449) and hepatic impairment (POP13450) studies. The interim study reports for the completed cohorts of the renal (severe renal impairment) and hepatic (mild) impairment studies will be included in the planned initial NDA.

Is the biopharmaceutical and clinical pharmacology plan adequate to support the NDA for the treatment of patients with myelofibrosis?

FDA Response to Question 6: It is the Agency's expectation that the NDA submission should be complete at the time of Original NDA submission. For clinical pharmacology studies that cannot be completed prior to NDA submission, appropriate restrictions should be included in proposed labeling. It is preferred that only final study reports are submitted for review. Interim study results should be included in the first cycle NDA review only if there is a serious safety signal that needs to be addressed in labeling.

Since the majority (76.9%) of the drug is excreted in the feces, a completed hepatic impairment study report should be included at the time of NDA submission or within 30 days after NDA submission. If this study cannot be completed prior to NDA filing, then appropriate labeling exclusions should be included to adequately label the restriction of SAR302503 in patients with hepatic impairment.

The feasibility of physiologically based PK (PBPK) modeling using SimCyp software (SIM0089) to evaluate the effects of a moderate CYP3A inhibitor (erythromycin), a CYP3A inducer (rifampin) will be a review issue.

Sanofi's Response June 25, 2013: The hepatic impairment study was planned sequentially: complete assessment of PK and safety in mild and then in moderate hepatically-impaired patients. The PK and safety of the mild hepatic impairment were assessed first in a group of 8 mild hepatic impaired subjects by comparing 8 healthy subjects matched with gender, age and body weight. The final report for this part of the study is planned for inclusion in the NDA. We understand that since the assessment of moderate cohort will not be completed at the NDA submission, the drug label will have a restriction for (b) (4) severe hepatic impairment.
Similarly, for the study in patients with renal impairment, the final report for the PK and safety assessments in patients with severe renal impairment compared healthy matches will be included in the NDA. The report on patients with moderate renal impairment, however, could be available within 30 days of submitting the original application. Please confirm the acceptability of submitting the final reports, with the original application, for (1) patients with mild hepatic impairment, and (2) patients with severe renal impairment, and submission of the final report for patients with moderate renal impairment within 30 days of submitting the original application.

Meeting Discussion June 27, 2013: The Agency finds the following acceptable:

- ***Submission for the final reports, with the original application, for (1) patients with mild hepatic impairment, and (2) patients with severe renal impairment***
- ***Submission of the final report for patients with moderate renal impairment within 30 days of submitting the original application.***

Question 7:

The assessment of the effect of SAR302503 on cardiac safety will include:

- Non-Clinical toxicology assessment and effects on the hERG channel current expressed in mammalian cells. No signal suggesting adverse impact on cardiac safety has been observed.

- A formal analyses of serial ECG data collected from the Phase 1 study (TED12037) which do not suggest any clinically meaningful QTcF prolongation induced by SAR302503 given up to 800 mg/day.

- A formal analysis of ECG data collected in the pivotal phase 3 study (EFC12153), in accordance with the recommendations from the QT-IRT group at the FDA.

A dedicated QTc study will be ongoing at time of filing the NDA (October 2013). The study has been initiated, taking into consideration the feedback from the QT-IRT group.

Does the Agency agree that the clinical study report for the ongoing dedicated QT study (TES13519) may be submitted post approval?

FDA Response to Question 7: This appears to be acceptable. The need for a dedicated QT study will be determined after review of ECG data collected thus far.

Sanofi's Response June 25, 2013: No further comment.

Meeting Discussion June 27, 2013: No discussion occurred.

2.5 Biostatistics

Question 8:
The analysis and presentation of efficacy and safety data is described in the CTD Statistical Analysis Plan submitted with the eData Submission Plan to the Agency on 19 February 2013 (Seq # 0178). The eData Submission Plan and CTD SAP and have been revised, based on FDA feedback received 24 April 2013 and are provided in [Attachments 1 and 2], respectively.

Does the Agency have any recommendations for additional analyses or data presentations to facilitate the assessment of safety and efficacy?

FDA Response to Question 8: For efficacy analyses, include analyses of duration of response and time to response for the primary and secondary efficacy endpoints in your NDA submission.

For pooled safety analyses, we recommend that you use the same MedDRA version and AE grading system (e.g., CTCAE) in the pooled dataset.

Sanofi's Response June 25, 2013 (revised response received June 27, 2013): The NDA will include analyses of duration of response and time to response for the primary endpoint (i.e. splenic response) and the key secondary endpoint (i.e. symptom response rate based on total symptom score).

Duration of splenic volume response (DR) (assessed by MRI/CT), a protocol pre-specified endpoint, is defined as the time from the date of the first response assessed by an Independent Review Committee (IRC), to the date of subsequent Progressive Disease (PD; defined as ≥ 25% increased spleen volume from baseline) assessed by an IRC, or death, whichever is earlier.

Time to splenic response (TR) is defined as time interval from randomization date to the date of the first response (defined as ≥ 35% reduction from baseline in spleen volume), assessed by an IRC.

Duration of symptom response (DSR) is defined as the time interval from initial response (total symptom score >=50% reduction from baseline) to the last valid total symptom score assessment before loss of response (defined as reduction < 50% reduction). Similar to that used for ruxolitinib, duration symptom response (DSR) was only be evaluated for 6 months duration.

Time to symptom response (TSR) is defined as time interval from randomization date to the date of the first response (defined as ≥ 50% reduction from baseline total symptom score).

For the pooled safety analyses, Sanofi will use the same MedDRA version for patient and healthy volunteer studies and CTCAE grading for patient studies only.

Meeting Discussion June 27, 2013: ***The sponsor will include some additional analyses for duration of response in the responders per primary endpoint, as well as an analysis of duration of response defined with an endpoint of loss of response.***
The sponsor will provide an additional analyses for the rate of the best splenic response.

2.6 Regulatory

Question 9:

The development of SAR302503 in patients with myelofibrosis includes the following studies:

- Phase 3 placebo-controlled, double-blind, study (EFC12153/JAKARTA) (N=289)
    - Conducted under a special protocol agreement with FDA
- Phase 2 study (ARD12181) in patients previously treated with ruxolitinib (N=70)
    - Interim report for filing the NDA is based on efficacy and safety data from 27 of the total 70 patients targeted for enrollment
    - A final report on 70 evaluable patients will be available during the review of the NDA
- Phase 1 dose-escalation study (TED12037; N=59) and an Phase 1/2 expansion study (TED12015; N=43) to evaluate long-term effects in patients continuing treatment from TED12037
- Phase 2 PK-PD study (ARD11936) (N=31)

In the Phase 3 study (EFC12153), there was a statistically significantly higher proportion of patients in both SAR302503 arms (36.5% and 39.2% in the 400 mg and 500mg arms, respectively) who achieved confirmed response when compared to placebo (1.0%), with a p value <0.0001 at 2.5% alpha level for each of the comparison. The proportion of patients with ≥ 35% reduction in spleen volume at 24 weeks relative to baseline, regardless of a second imaging confirmation 4 weeks later, was higher in both SAR302503 arms (46.9% and 49.5% in the 400 mg and 500 mg arms, respectively) when compared to placebo (1.0%), for each of the comparisons. Similarly, the proportion of patients who achieved ≥50% reduction in TSS was statistically significantly higher in the treatment arms (36.3% and 33.7% in the 400 mg and 500 mg arms, respectively) compared to placebo (8.1%), with a p value <0.0001 at 2.5% alpha level for each of the comparison. Gastro-intestinal adverse events, including diarrhea, vomiting and nausea were the most frequently TEAEs reported in both SAR302503 treatment arms by comparison to placebo. The most common hematological abnormalities were anemia and thrombocytopenia.

In patients previously treated with ruxolitinib (ARD12181), a response rate of 40% was observed in the per-protocol population at the end of 3 cycles. The proportion of patients with a ≥50% reduction in TSS was 19.2%. The safety profile was similar to that observed in the Phase 3 study (EFC12153).

Question 9a: Does the Agency agree that the efficacy and safety data from the Phase 3 study (EFC12153) together with the efficacy and safety data from the Phase 2 (ARD11936), and Phase 1/2 [TED12037 and TED12015]) studies are sufficient to support the NDA for the treatment of patients with intermediate or high-risk myelofibrosis?

FDA Response to Question 9a: Your proposal appears acceptable. However, the adequacy of the pivotal Phase 3 trial and the supportive Phase 1 and 2 trials in support of the proposed indication will be determined upon review of the NDA submission.

Sanofi's Response June 25, 2013 (revised response received June 27, 2013: The revised proposed label indication is as follows:

(b) (4)

Meeting Discussion June 27, 2013: Sponsor clarified (b) (4)

Question 9b: Does the Agency agree tha (b) (4)

(b) (4)

(b) (4)

Sanofi's Response June 25, 2013 (revised response received June 27, 2013): Sanofi acknowledges the Agency's comment and we will request a separate meeting with the Agency when full data are available.

In accordance with this agreement with the Agency, Sanofi will submit a revised eCTD SAP.

Meeting Discussion June 27, 2013: The sponsor's proposal is acceptable.

Question 9c: If so, does the Agency agree that the final report may be filed to the NDA during the review process?

FDA Response to Question 9c: No. The Agency requires submission of complete study reports and datasets at the time of NDA submission for the following clinical trials: Phase 3 clinical trial (EFC12153), Phase 2 clinical trial (ARD11936), and Phase 1/2 clinical trials (TED12037 and TED12015).

Sanofi's Response June 25, 2013 (revised June 27, 2013): Sanofi acknowledges the Agency's comment and confirms that the studies mentioned above will be used to support the proposed indication.

Meeting Discussion June 27, 2013: No further discussion occurred.

Clinical Site Investigations

Question 10:
The tabular summary of site information for use by OSI is based on the requirements outlined in the December 2012 draft Guidance for Industry entitled, "Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning." This information will be provided for the Phase 3 (EFC12153) and Phase 2 (ARD11936) studies in patients not previously treated with a JAK2 inhibitor, and Phase 2 (ARD12181) study in patients previously exposed to ruxolitinib.

The tabular summary provided in [Attachment 4] is an example, using data from EFC12153, of the level of detail being proposed for all three studies.

Does the Agency agree that the level of detail provided for the by site information for the Phase 3 (EFC12153) and Phase 2 (ARD11936) studies in patients with myelofibrosis, and the Phase 2 study in patients with myelofibrosis previously treated with ruxolitinib (ARD12181) is sufficient to assist OSI with their selection of sites for auditing?

FDA Response to Question 10: Yes. However, additional information may be requested if any concerns arise during the review.

Sanofi's Response June 25, 2013: No further comment.

Meeting Discussion June 27, 2013: No discussion occurred.

ADDITIONAL CLINICAL COMMENTS:

1. Describe the method used to determine the spleen volume based on MRI or CT scans. We recommend that you include the individual dimensions of the spleen (cranio-caudal, anterior-posterior, and transverse) for each measurement of spleen volume.

Sanofi's Response June 25, 2013 (revised June 27. 2013):

Central Image Evaluation Response
Spleen volume measurements were obtained by manual segmentation of the spleen images by trained imaging technologists and/or radiologists to form a stack of transverse 2D regions-of-interest (ROIs). The reported volume is the sum of the products of the areas of the ROIs and the image slice thickness. As such, the reported values are based on volumetric measurements and not linear approximations. The tool used to perform the measurements is a commercial, off-the-shelf (COTS) software program with FDA 510(k) certification, Medical Image Merge (MIM). One of the 510(k) requirements was specific to contour (i.e. ROI) generation. The ROI output of the tool is used extensively in the clinic for radiotherapy planning and has been clinically evaluated in addition to vendor tested, validated and FDA reviewed for 510(k) approval.

The method of calculation supporting spleen volume is an actual volume measurement done by adding the ROIs from manual segmentation of the spleen images and the image slice thickness. The approximation of spleen volume using the individual measurement dimensions was not performed.

In the context of this methodology used by the Sanofi (b) (4) ***which was pre-specified in the Medical Imaging Charter, we would like to discuss how Sanofi can facilitate the validation and reproducibility of the spleen volume by the Agency.***

Meeting Discussion June 27, 2013: The sponsor agrees to provide the extracted splenic dimensions (cranio-caudal, anterior-posterior, and transverse) to allow additional exploratory analyses.

2. Discuss your timelines for submission of longer-term efficacy and safety follow-up for clinical trial EFC12153.

Sanofi's Response June 25, 2013 (revised June 27, 2013): Updated safety data will be provided with the day 120 safety update report, as well as annually with the DSUR (reporting period November 29 – November 28.

The final analysis for PFS and OS will be conducted according to protocol pre-specified criteria when 126 death events have been reached. Based on the death rate at time of data cut-off for the primary endpoint, the 126th death is expected in March 2017.

Meeting Discussion June 27, 2013: No discussion occurred.

3. Discuss the occurrence of rebound or withdrawal syndromes following SAR302503 discontinuation.

Sanofi's Response June 25, 2013: Sanofi will provide an evaluation of patients who temporarily or permanently interrupted treatment. This evaluation will include the

available information on occurrences, if any, of rebound and withdrawal syndromes in the clinical program.

Meeting Discussion June 27, 2013: The sponsor's proposal is acceptable.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

In the appropriate clinical pharmacology sections of the eCTD include the following**:**

- Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.

  Sanofi's Response June 25, 2013 (revised June 27, 2013): The NDA will include pooled analysis datasets from healthy volunteer studies for all relevant domains related to safety (adverse events, non-PK laboratory values, electrocardiograms) as well as disposition, demographics, and exposure as requested by the Agency. For studies that are not included in the pooled analysis, analysis datasets for individual studies will be provided.

  Meeting Discussion June 27, 2013: The sponsor's proposal is acceptable and column IDs for study number and dose should be included in the data set.

- Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

  Sanofi's Response June 25, 2013: No further comment.

  Meeting Discussion June 27, 2013: No discussion occurred.

- Provide a table listing of patients with renal or hepatic impairment who have received SAR302503, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.

  Sanofi's Response June 25, 2013: No further comment.

  Meeting Discussion June 27, 2013: No discussion occurred.

- We encourage you to refer to the following pharmacometric data and models submission guidelines (http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm). For any population PK models all datasets used for model development and validation should

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

Sanofi's Response June 25, 2013: Sanofi acknowledges and data will be provided as requested.

Meeting Discussion June 27, 2013: No discussion occurred.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 25, 2013 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

- The content of a complete application was discussed. However, the sponsor will notify the Agency if there will be a separate pre NDA CMC meeting.

- The sponsor proposes to submit a complete application at the time of initial submission with the exception of two items:
  1. Final study report for 6 month mouse carcinogenicity study will be submitted within 30 days of submission. The sponsor stated that they will include a draft report with the initial submission.
  2. The final study report for patients with moderate renal impairment will be submitted within 30 days of submission.

  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.

- The Agency reiterated that based on the information currently available, the Agency does not believe that a REMS will be necessary. The Agency will make a final determination for the need for REMS during the review of the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  - Final Carcinogenicity study report for 6 month mouse study
  - Final PK study report for patients with moderate renal impairment

  Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT - BIOMETRICS
  NDANUMBER: LATE COMPONENT - CLINICAL
  NDANUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
  NDA NUMBER: LATE COMPONENT - NONCLINICAL
  NDA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Further, under the Food and Drug Administration Safety and Innovation ACT (FDASIA), sponsors must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.

- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

Sanofi will inform the Agency of their plans for a CMC only Pre-NDA meeting.

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

ROMEO A DE CLARO
07/10/2013